2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of ethylene glycol and propylene glycol and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for ethylene glycol and propylene glycol based on toxicological studies and epidemiological investigations.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

The general population may be exposed to either ethylene glycol or propylene glycol. Although the two compounds are similar in structure and chemical characteristics, they do not share the same degree of toxicity. The two compounds are presented together in this document because they share common physical properties, and can be used interchangeably in a number of industrial applications. Ethylene glycol is widely sold in grocery stores and in automobile supply, discount, drug, and other stores throughout the United States for general use as an antifreeze/coolant in automobile radiators. Additionally, it is used in the manufacturing or blending of polyester products; aircraft and runway de-icing fluids; heat transfer fluids used in heating, ventilation, and air conditioning systems; polyester resins; humectants; alkyd-type resins; plasticizers; electrolytic capacitors; low freeze dynamite; and brake and shock solutions (Wiener and Richardson 1988). Ethylene glycol is also used in the production of artificial mists or fogs (NIOSH 1994). Propylene glycol is designated as a Generally Recognized As Safe (GRAS) additive by the Food and Drug Administration (FDA) and is widely used in commercial formulations of foods, drugs, and cosmetics (Morshed et al. 1988). Propylene glycol is used as a de-icer, and in heat transfer fluids. It is also an ingredient of many products that are used to produce artificial smoke or mist for theatrical productions, fire safety training, or rock concerts.

Of the two glycols, ethylene glycol exhibits a much higher degree of toxicity than propylene glycol. Toxicity information for each compound is presented separately, within sections, below.

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Dermal exposure, through activities such as changing antifreeze, is the most likely route of exposure to ethylene glycol, but dermal exposure is not likely to lead to toxic effects. Only oral exposure, through accidental or intentional ingestion, is likely to lead to such effects, and then only if a sufficient amount is swallowed at one time. A review of the literature for ethylene glycol indicated that the stages of oral ethylene glycol poisoning in humans are well understood and documented. There is adequate knowledge of ethylene glycol metabolism to permit successful treatment of ethylene glycol intoxication, and substantial information concerning pathology and pathophysiology of the organ systems involved is available. Although the majority of the studies in humans represent descriptions of case studies of accidental or intentional poisoning, or exposure in industrial settings, they have been collected for a period of over 60 years. Animal studies corroborate human findings and were used to provide quantitative data to support observations made in humans.

Oral exposure to the small amounts of propylene glycol found in foods and drugs is unlikely to cause toxic effects. Dermal exposure to propylene glycol, through cosmetics or drugs, or inhalation of synthetic smoke or mist, may be more frequently associated with reported reactions. Propylene glycol induces remarkably fewer adverse effects in both humans and animals than does ethylene glycol. Data describing either human or animal effects after exposure to propylene glycol were not as prevalent as those found for ethylene glycol. Human data came from case reports of clinical studies, adverse reactions to medical treatment, or accidental exposure. Animal data generally support those effects, or lack thereof, observed in humans.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites or other areas where they may be exposed to ethylene glycol or propylene glycol, the information in this section is organized by chemical, and then by health effect-death, systemic, immunological and lymphoreticular, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the

studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgement may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to,classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. These distinctions are intended to help the users of this document identify the levels of exposure at which adverse health effects start to appear. LOAELs or NOAELs should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these differences to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites or other sites of exposure may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for both ethylene glycol and propylene glycol. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify target organs(s) of effect or the most sensitive health effects(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure. Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these

techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for heahh effects that are delayed in development or result from repeated acute insuhs, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Information regarding health effects of ethylene glycol following inhalation exposure is Iimited. Health effects in humans were found in only a few studies (Bond et al. 1985; Triosi 1950; Wills et al. 1974). Animal studies were described by Tyl (1985, 1988a). Information regarding health effects of propylene glycol following inhalation exposure is also limited. No studies of health effects in humans were found. Studies in animals were few (Konradova et al. 1978; Robertson et al. 1947; Suber et al. 1989).

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to ethylene glycol. Therefore, no LOAELs for death following inhalation exposure could be established. Based on the absence of data in the literature, it is unlikely that sufficient amounts of ethylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

No studies were located regarding death in humans following inhalation exposure to propylene glycol. Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (doses not further specified) (Robertson et al. 1947). Thirteen of the monkeys died or were killed when ill during the course of the experiment (Robertson et al. 1947). Based on the relative lack of data in the literature, it is unlikely that sufficient amounts of propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

The LOAEL value from the study by Robertson et al. (1947) for death in monkeys after inhalation exposure to propylene glycol is recorded in Table 2-2 and plotted Figure 2-2.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hepatic, endocrine, dermal, ocular, body weight, or metabolic effects in humans or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, dermal, ocular, or metabolic effects in animals after inhalation exposure to ethylene glycol. No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans, or cardiovascular, musculoskeletal, dermal, ocular, or metabolic effects in animals after inhalation exposure to propylene glycol. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Throat and upper respiratory tract irritation was observed after 1.5 minutes of inhalation exposure of volunteers exposed to a concentration of 55 ppm ethylene glycol (Wills et al. 1974). Doses above 79 ppm were very irritating and were not tolerated for more than 1 minute (Wills et al. 1974). Because of the low vapor pressure of ethylene glycol, however, the potential inhalation hazard in the vicinity of a hazardous waste site is considered to be low (Siew et al. 1975a), although small quantities of ethylene glycol could be inhaled in contaminated dust.

Studies assessing adverse respiratory effects after acute or intermediate inhalation exposure of animals to propylene glycol are inconclusive. The effects of acute inhalation exposure to 10% concentrations of propylene glycol for 20 and 120 minutes in rabbits showed an increased number of degenerated goblet cells in tracheal lining (Konradova et al. 1978). However, the observations made in rats after an intermediate inhalation exposure to propylene glycol did not support those findings. Rats which inhaled 321 ppm of propylene glycol over 90 days had thickened respiratory epithelium with enlarged goblet cells (Suber et al. 1989). Nasal hemorrhaging was also present in rats exposed to a lower dose of 51 ppm propylene glycol, probably caused by dehydration. In rhesus monkeys and rats, continuous

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Systemic							
1	Human	15 min	Resp		55 M (throat and upper respiratory tract irritation)		Wills et al. 1974
2	Rat (CD)	10 d Gd 6-15 6 hr/d	Hepatic	400 F	1000 F (increased absolute and relative liver weight)		Tyl 1985
			Renal	1000 F			
			Bd Wt	1000 F			
3	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	1000 F			Tyl 1985
			Renal	1000 F			
			Bd Wt	60 F	400 F (reduced body weight and weight gain)		
4	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	985 F			Tyl 1988a
			Renal	197[b] F	394 F (increased absolute kidney weight)		
			Bd Wt	985 F			
5	Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	827 F			Tyl 1988a
			Renal	827 F			
			Bd Wt		827 F (reduced maternal weight gain)		
Reproductive							
6	Rat (CD)	10 d Gd 6-15 6 hr/d		1000			Tyl 1985

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
7	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		60			400	(postimplantation loss)	Tyl 1985
8	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		985					Tyl 1988a
9	Mouse (CD-1)	10 d Gd 6-15 6 hr/d					827	(postimplantation loss)	Tyl 1988a
Developmental									
10	Rat (CD)	10 d Gd 6-15 6 hr/d		60	400	(reduced ossification of the humerus, zygomatic arch, and metatarsals and proximal phalanges of the hindlimb)			Tyl 1985
11	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		60	400	(decreased fetal body weight, increased incidence of variations)			Tyl 1985
12	Mouse (CD-1)	10 d Gd 6-15 6 hr/d		394	985	(reduced fetal body weight; increased skeletal variations)			Tyl 1988a
13	Mouse (CD-1)	10 d Gd 6-15 6 hr/d			827	(reduced fetal body weight; increased skeletal variations)			Tyl 1988a
INTERMEDIATE EXPOSURE									
Systemic									
14	Human	30 d 20-22 hr/d	Hemato Renal	19 M 19 M					Wills et al. 1974

TABLE 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Neurological						
15	Human	30 d 20-22 hr/d			19M (slight headache, low backache)		Wills et al. 1974

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an acute inhalation minimal risk level (MRL) of 0.5 ppm; NOAEL was multiplied by an exposure factor of 6/24 hours, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation

Acute (≤14 days)

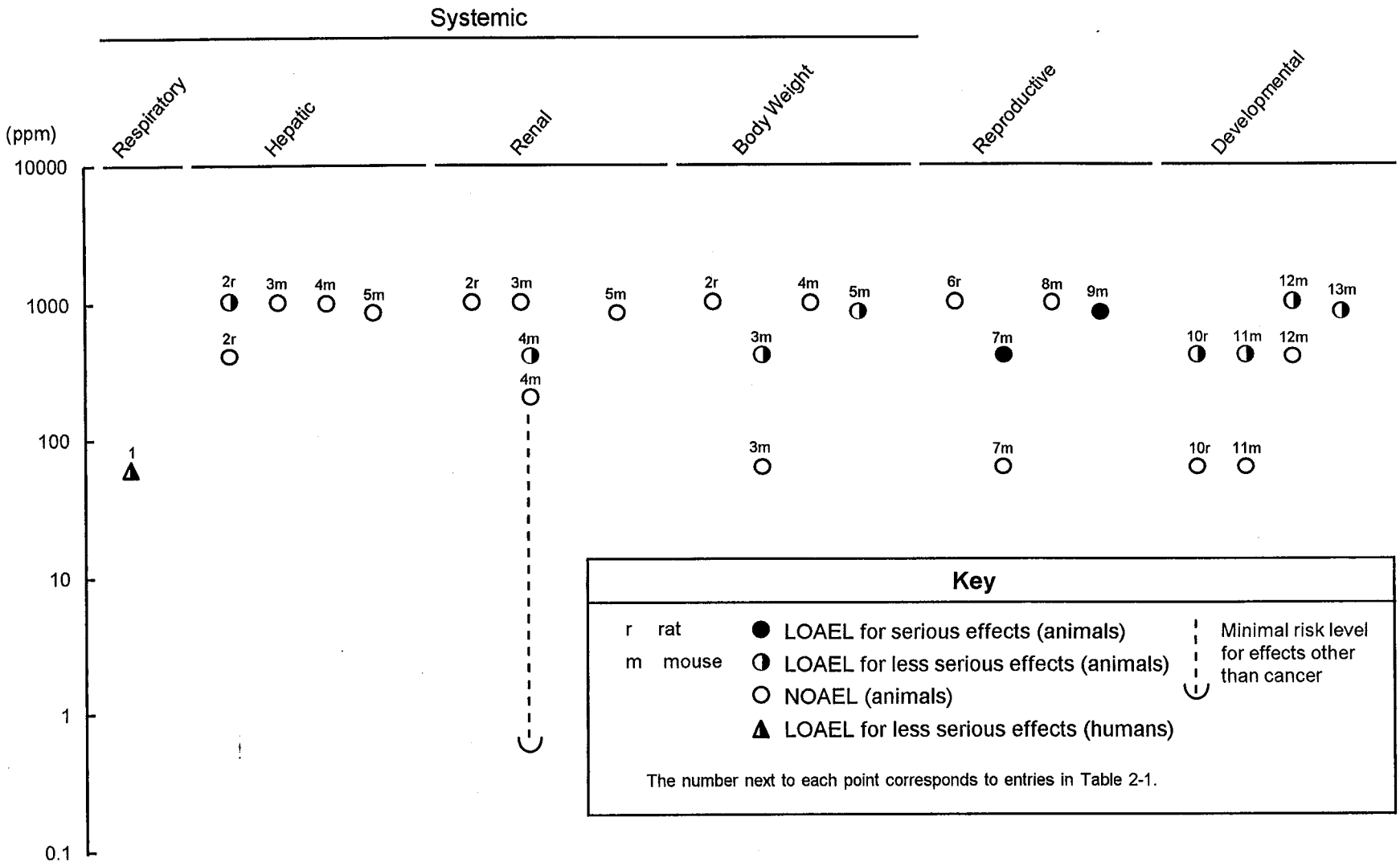


Figure 2-1. Levels of Significant Exposure to Ethylene Glycol - Inhalation (continued)

Intermediate (15-364 days)

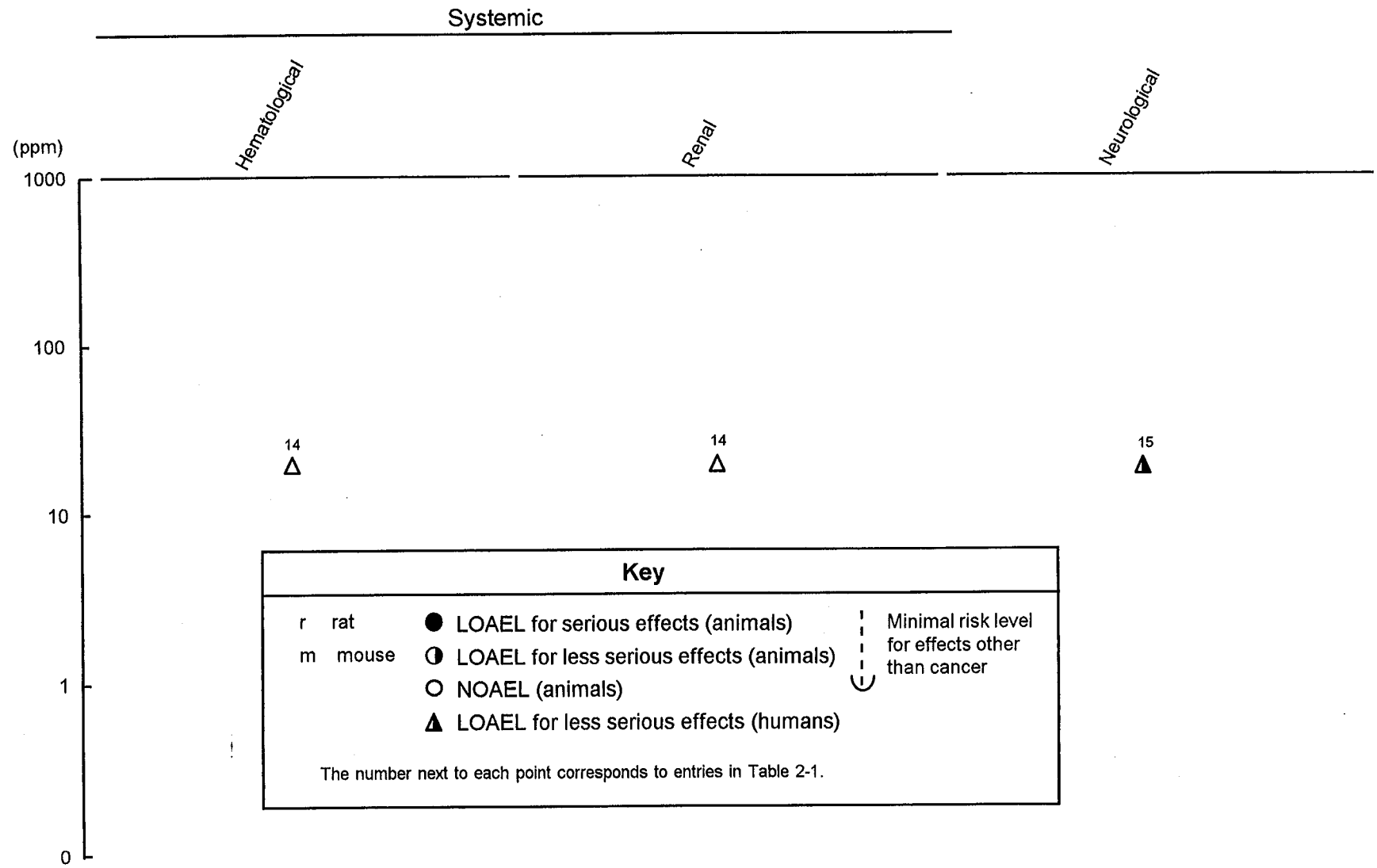


TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
1	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp		51[b] (nasal hemorrhaging)		Suber et al. 1989
			Hemato	51 F	321 F (decreased white blood cells, and lymphocytes in females)		
				51 M	321 M (decreased sorbitol dehydrogenase, gamma glutamyl transferase)		
			Hepatic	707			
			Renal	51	321 (decreased kidney weight)		
			Bd Wt	51 F	321 F (decreased body weight)		
Immunological/Lymphoreticular							
2	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		707			Suber et al. 1989
CHRONIC EXPOSURE							
Systemic							
3	Monkey (Macacus Rhesus)	13 mo continuous	Resp	112			Robertson et al. 1947
			Gastro	112			
			Hemato		112 (increased hemoglobin)		
			Hepatic	112			
			Renal	112			
			Endocr	112			
			Bd Wt	112			

TABLE 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
4	Rat (NS)	18 mo continuous	Resp	112			Robertson et al. 1947
			Hepatic	112			
			Renal	112			
			Bd Wt		112M (50% increase in body weight)		
	Immunological/Lymphoreticular						
5	Monkey (Macacus Rhesus)	13 mo continuous		112			Robertson et al. 1947
6	Rat (NS)	18 mo continuous		112			Robertson et al. 1947
	Reproductive						
7	Rat (NS)	18 mo continuous		112			Robertson et al. 1947

[a]The number corresponds to entries in Figure 2-2.

[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 0.009 ppm; LOAEL divided by an uncertainty factor of 1,000 (10 for extrapolation from animals to humans,10 for use of a LOAEL, and 10 for human variability) and multiplied by 6/24 and 5/7 to adjust for intermittent exposure of 6 hours/day, 5 days/week.

Bd Wt = body weight; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation

Intermediate (15-364 days)

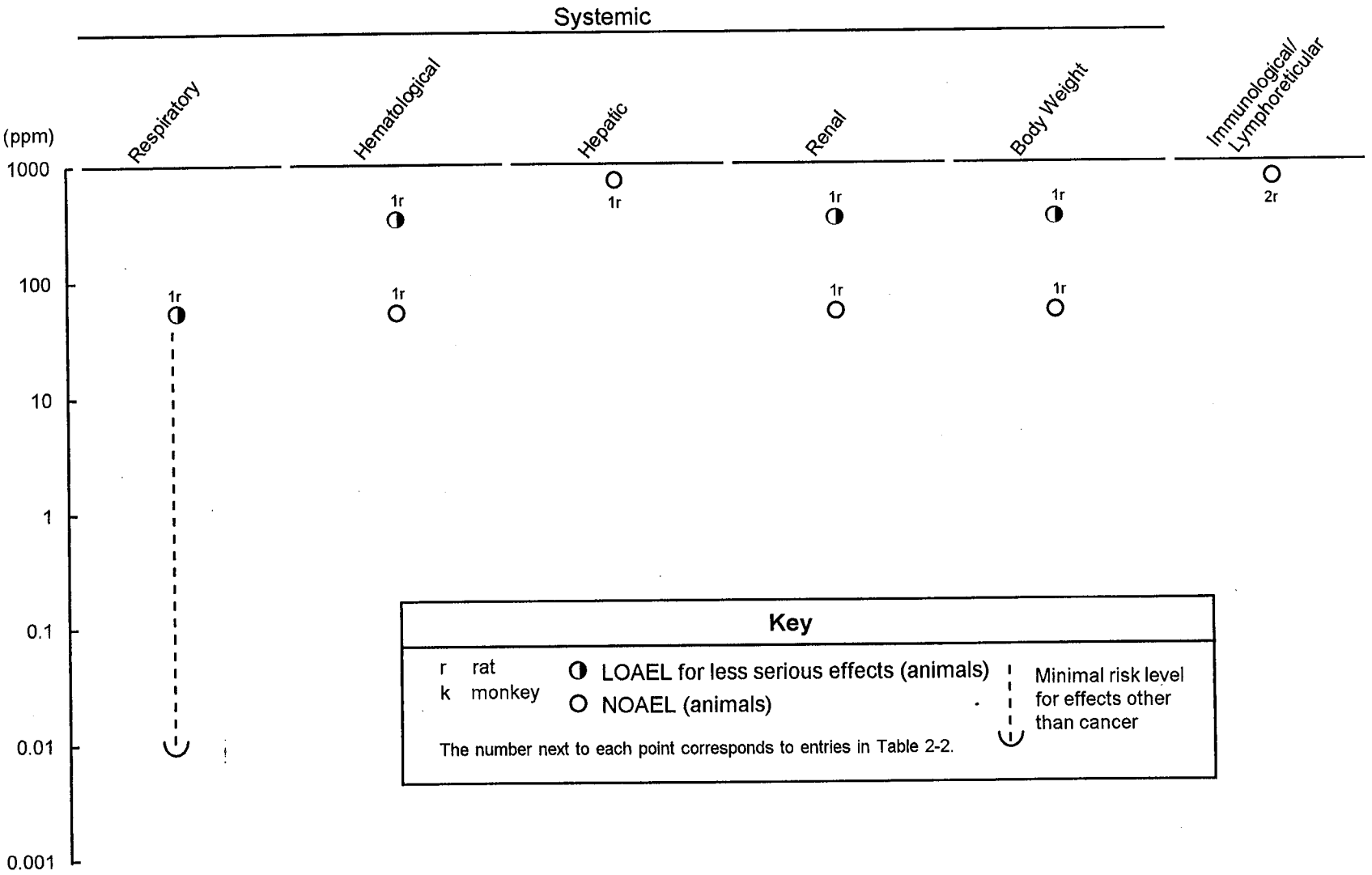
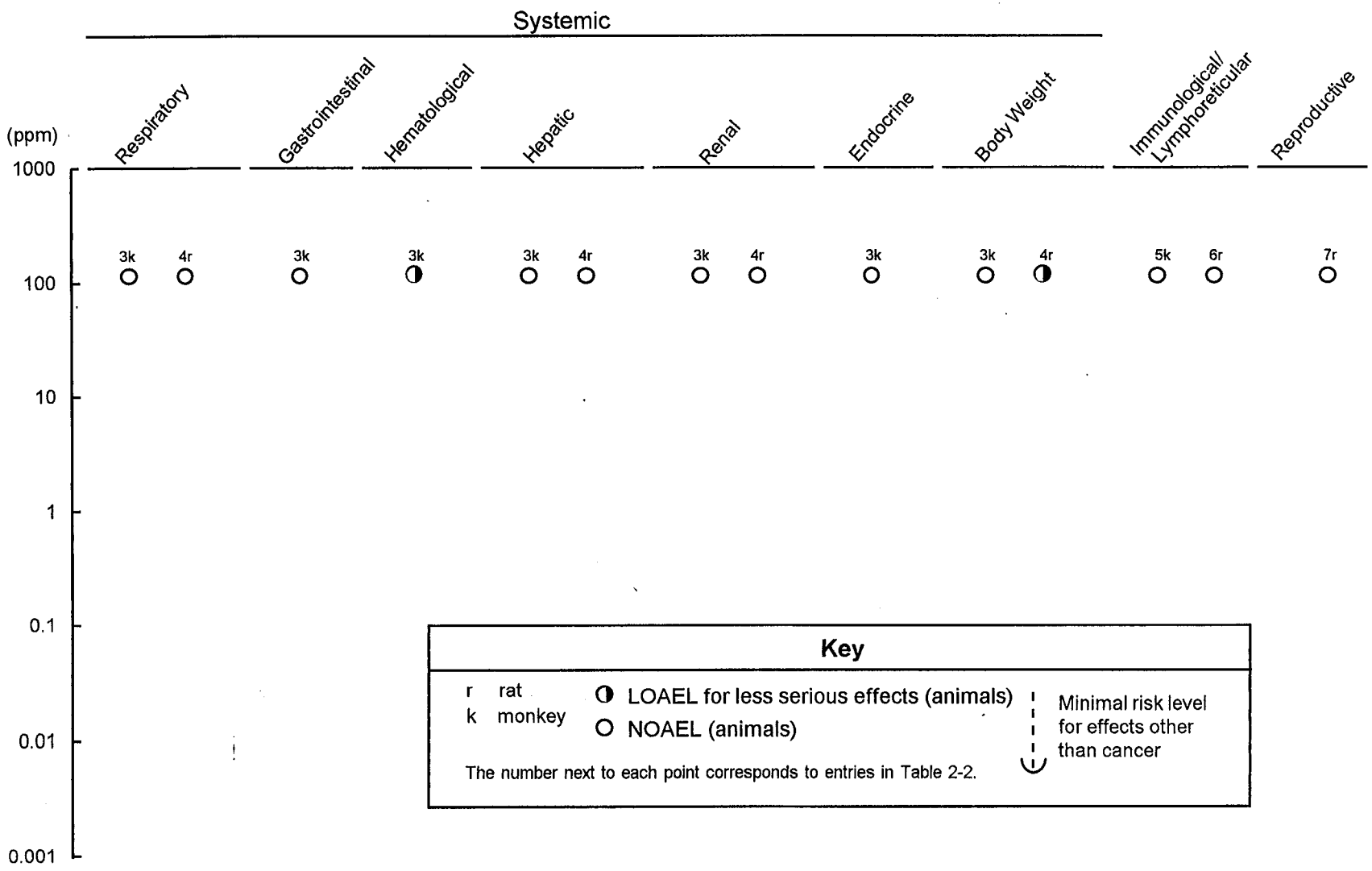


Figure 2-2. Levels of Significant Exposure to Propylene Glycol - Inhalation (continued)

Chronic (≥365 days)



exposure to concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the respiratory system (Robertson et al. 1947). These studies do not indicate a basis for concern because comparable exposure conditions do not occur for the general population.

Gastrointestinal Effects. In rhesus monkeys and rats, continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the gastrointestinal system (Robertson et al. 1947).

Hematological Effects. After inhalation exposure to mean daily concentrations of 7-19 ppm ethylene glycol for 20-22 hours per day for 4 weeks, a group of 20 volunteers showed no significant alterations of hematologic parameters, including hematocrit, hemoglobin, and differential counts (Wills et al. 1974). The authors speculate that an insufficient amount of vaporized ethylene glycol was absorbed through the epithelium of the respiratory tract to cause toxicity, although total absorption of inhaled aerosols would be expected.

Limited information was available on hematological effects of propylene glycol. The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells (RBC). After intermediate inhalation exposure to 321 ppm propylene glycol, female rats had decreased white blood cell (WBC) counts, while exposure to 707 ppm of propylene glycol caused decreased mean corpuscular hemoglobin concentrations and white blood cell counts; no dose-related changes in RBCs were observed in male rats under the same regimen (Suber et al. 1989). In rhesus monkeys, continuous exposure to concentrations of propylene glycol in air up to 112 ppm for 13 months caused increased hemoglobin counts compared to the control animals (Robertson et al. 1947). These results indicate that there may, be species differences with regard to the effect of propylene glycol on red blood cells.

Hepatic Effects. Rats exposed to 1,000 ppm ethylene glycol on gestational day (Gd) 6-15 by whole body inhalation procedures exhibited increased absolute and relative liver weight; whereas mice. exposed to 827 ppm ethylene glycol under the same regimen showed no hepatic effects (Tyl 1985, 1988a).

The results from animal studies show that there are no adverse hepatic effects in rats after intermediate inhalation exposure to 707 ppm of propylene glycol (Suber et al. 1989). In rhesus monkeys and rats,

continuous exposure to air concentrations of propylene glycol up to 112 ppm for 13-18 months caused no adverse effects on the hepatic system (Robertson et al. 1947). Based on these findings, it can be assumed that chronic exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects in people living in the area.

Renal Effects. After inhalation exposure to mean daily concentrations of 7-19 ppm ethylene glycol for 20-22 hours per day for 4 weeks, a group of 20 volunteers showed no significant alterations of renal parameters (Wills et al. 1974).

Mice exposed to aerosolized ethylene glycol by nose-only procedures on Gd 6-15 exhibited a decrease in absolute kidney weight at 394 ppm, although no treatment-related microscopic lesions were observed (Tyl 1988a).

Intermediate inhalation exposure of rats to 707 ppm propylene glycol did not cause adverse renal effects (Suber et al. 1989), although kidney weight was reduced at 321 ppm in males and females. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycoi up to 112 ppm for 13-18 months caused no adverse effects on the renal system (Robertson et al. 1947). These results indicate that exposure to low levels of propylene glycol that may be present at hazardous waste sites is not likely to cause adverse renal effects in the human population living in the vicinity.

Endocrine Effects. In rhesus monkeys and rats, continuous exposure to concentrations of propylene glycol up to 112 ppm for 13-l 8 months caused no adverse effects on the endocrine system (Robertson et al. 1947).

Body Weight Effects. Body weight does not appear to be a sensitive indicator of ethylene glycol toxicity. Only one of the studies in animals which identify systemic effects shows adverse effects on body weight. Pregnant CD-l mice showed a decrease in body weight and body weight gain after whole body inhalation exposure to 400 ppm ethylene glycol on Gd 6-15, but nose-only exposure to doses up to 985 ppm produced no change in body weight or body weight gain (Tyl 1988a).

Rhesus monkeys continuously exposed to air concentrations of propylene glycol up to 112 ppm for 13 months exhibited no adverse body weight effects, whereas rats exposed for 18 months under the same conditions exhibited a 50% decrease in body weight (Robertson et al. 1947). Intermediate inhalation exposure of female rats to 321 ppm caused decreased body weight (Suber et al. 1989).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located specifically regarding adverse immunological effects in humans or animals after inhalation exposure to ethylene glycol. However, after intermediate inhalation exposure of 20 volunteers to 7-19 ppm ethylene glycol, no significant alterations in lymphocyte or monocyte counts were noted (Wills et al. 1974).

Currently, there is no evidence that acute exposure to high concentrations of ethylene glycol adversely affects immunological functions. Intermediate exposure to low concentrations of ethylene glycol that may be present in the vicinity of hazardous waste sites is not likely to produce adverse immunological effects in populations residing in the area.

No studies were located specifically regarding adverse immunological effects in humans or animals after inhalation exposure to propylene glycol.

Twenty-nine monkeys were continuously exposed to propylene glycol vapor over a period of 13 months, at doses of 32-112 ppm (Robertson et al. 1947). There was no effect on the spleen. Similarly, rats exposed to 55-l 12 ppm propylene glycol vapor continuously for 18 months showed no effect on the spleen (Robertson et al. 1947). Young, healthy adult Sprague-Dawley rats divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 5 1, 321, or 707 ppm propylene glycol, respectively (Suber et al. 1989). The fourth group (control group) was exposed to humidified, filtered room air. There was no effect on spleen weight. -’

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in each species and duration category for propylene glycol after inhalation exposure are reported in Table 2-2 and plotted in Figure 2-2.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in animals after inhalation exposure to ethylene glycol. Little information was available on neurological effects of inhaled ethylene glycol in humans. A group of 22 volunteers, exposed for 20-22 hours per day for 4 weeks. to an average concentration of 7-19 ppm aerosolized ethylene glycol, exhibited only slight headache and backache as a result (Wills et al. 1974). No effects were seen in a battery of psychological tests conducted on these subjects (Wills et al. 1974).

No studies were located regarding neurological effects in humans or animals after inhalation exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-1, and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to ethylene glycol.

Whole body exposure of pregnant CD-l mice to 60-1,000 ppm aerosolized ethylene glycol for 6 hours a day on Gd 6-15 caused a decrease in the number of live implants at 400 ppm, but no effect on reproductive parameters was observed in CD rats dosed under the same regimen (Tyl 1985). The study was limited by the possible confoundin,0 factor of ingestion of ethylene glycol from the fur of exposed animals (in grooming). In a companion study, nose-only exposure of CD-l mice to 197-985 ppm aerosolized ethylene glycol using the same study design resulted in no postimplantation loss (Tyl 1988a). An additional study in CD-l mice, using nose-only procedures and the same exposure regimen, showed increased postimplantation loss at 827 ppm (Tyl 1988a).

No studies were located regarding reproductive effects in humans after inhalation exposure to propylene glycol.

White rats exposed continuously to a concentration of 55-112 ppm propylene glycol for 18 months showed no adverse effects on the ability to produce live young, or on survival of the offspring (Robertson et al. 1947).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l. The NOAEL value for reproductive effects in rats for the chronic-duration category for propylene glycol after inhalation exposure is reported in Table 2-2 and plotted in Figure 2-2.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to ethylene glycol.

Whole body exposure of pregnant CD-l mice to 60-1,000 ppm aerosolized ethylene glycol for 6 hours a day on Gd 6-15 caused a decrease in the number of live implants and in the weight of live fetuses, and an increase in the incidence of external, visceral, and skeletal malformations (Tyl 1985). The study was limited by the possible confounding factor of ingestion of ethylene glycol from the fur of exposed animals (in grooming). In a companion study, nose-only exposure to 197-985 ppm aerosolized ethylene glycol using the same study design resulted in reduced live fetal body weight at 985 ppm, but no increase in malformation incidence at any dose (Tyl 1988a). An additional study in CD-l mice, using nose-only procedures and the same exposure regimen, showed reduced fetal body weight at 827 ppm (Tyl 1988a). Similar studies conducted in Sprague-Dawley rats revealed reduced ossification at some sites in the axial skeleton after whole body exposure to 400 ppm aerosolized ethylene glycol (Tyl 1985).

No studies were located regarding developmental effects in humans or animals after inhalation exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category for ethylene glycol after inhalation exposure are reported in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding in viva genotoxic effects in humans or animals after inhalation exposure to ethylene glycol or propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

One epidemiologic study on renal cancer mortality examined the work and health histories of 1,666 employees of a chemical plant and found no elevation in the odds ratio for workers exposed to ethylene glycol (Bond et al. 1985), although the sample size was quite small. Exposure was presumed to be by inhalation.

No studies were located regarding cancer effects in animals after inhalation exposure to ethylene glycol.

Because of information available, it is reasonable to conclude that inhalation exposures to ethylene glycol incurred from waste site sources pose negligible risks of cancer.

No studies were located regarding cancer effects in humans or animals after inhalation exposure to propylene glycol.

2.2.2 Oral Exposure

Ethylene glycol is a colorless, water-soluble liquid with a sweet taste and little or no odor, most commonly used as an antifreeze fluid. The ready availability of antifreeze mixtures makes ethylene glycol intoxication a significant medical and veterinary problem. Antifreeze mixtures c+t.in up to 95% ethylene glycol (Mallya et al. 1986; Siew et al. 1975a). The exposure route most commonly associated with adverse effects is oral ingestion.

Propylene glycol is also a clear, practically odorless and tasteless liquid that is slightly syrupy at room temperature. Oral exposure to propylene glycol occurs through ingestion of foods, since propylene

glycol is approved for use as a food additive. Ingestion by humans is not frequently associated with adverse effects.

2.2.2.1 Death

The American Association of Poison Control Centers reported nine and five fatalities for 1989 and 1990, respectively, due to ethylene glycol ingestion (Litovitz et al. 1990, 1991). Several other fatal ethylene glycol poisonings have been reported in earlier studies. Seven case reports of deaths in humans resulting from accidental or intentional ingestion of ethylene glycol or antifreeze containing 99% ethylene glycol have been located (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsen et al. 1984; Siew et al. 1975a; Zeiss et al. 1989). In one case, the dose of ingested ethylene glycol was known, 4,071 mg/kg (Siew et al. 1975a). The 22-year-old male who ingested 300 mL of antifreeze lapsed into a coma 24 hours after hospital admission and died 24 hours later. A dose of 7,850 mg/kg can be estimated in the case of a 73-year-old male who consumed 500 mL of 95% ethylene glycol and died of myocardial failure after 68 hours (Gordon and Hunter 1982). Two deaths involved an 18-year-old male who died of brain stem failure (Godolphin et al. 1980) and a 29-year-old male who died of renal failure (Zeiss et al. 1989). The accidental death of a 53-year-old female patient occurred following dialysis with a solution accidentally prepared with ethylene glycolcontaminated water (Anonymous 1987). After developing metabolic acidosis, the patient lapsed into irreversible shock and coma, and died 24 hours after'dialysis. Twelve other fatal cases of accidental or intentional poisoning have been reported in similar epidemic-like occurrences (Karlson-Stilber and Persson 1992; Walton 1978). The amount of ingested ethylene glycol ranged from 150 to 1,500 mL (2,379-23,786 mg/kg), except for 7 cases in which the amount was not known.

Male Wistar rats with intact livers were given 12,900 mg/kg ethylene glycol in a single oral dose, and had a 55% mortality rate within 48 hours (Richardson 1973). In the same study, partially hepatectomized male Wistar rats with l/3 and 2/3 hepatectomies had 27% and 13% mortality, respectively, indicating decreased metabolism of ethylene glycol, decreased production of toxic metabolite, and subsequent death (Richardson 1973). Female Fischer 344 rats exhibited an oral LD_{50} of 4,000 mg/kg (Clark et al. 1979). Pregnant CD-l mice given 11,090 mg/kg/day ethylene glycol orally on gestational days (Gd) 7-14 showed 10% mortality (Schuler et al. 1984), whereas pregnant rabbits exhibited 42% mortality after receiving 2,000 mg/kg/day ethylene glycol orally on Gd 6-19 (Tyl et al. 1993). Male Fischer 344/N rats fed 2,500 mg/kg/day ethylene glycol had 40% mortality

after 13 weeks, whereas similarly treated females did not die (Melnick 1984). Male Sprague-Dawley rats given 500 or 2,000 mg/kg/day ethylene glycol in the feed during a 2-year study showed 100% mortality in each group after 18 months (Blood 1965). Female rats in the same study exhibited 100% mortality only in the 2,000 mg/kg/day group (Blood 1965). Similarly, male Fischer 344 rats given 1,000 mg/kg/day ethylene glycol in the feed all died within 16 months (DePass et al. 1986a; Woodside 1982). Similar findings occurred in cats that were administered ethylene glycol at 4,440 mg/kg orally. All animals developed loss of reflexes, convulsions, central nervous system depression (symptoms not specified), and coma. All animals died 20-36 hours after exposure unless treated with ethanol (Penumarthy and Oehme 1975). Ethylene glycol induced a similar, lethal toxicity in dogs given 4,880 mg/kg orally (Beckett and Shields 1971), whereas in another study, 17-100% of the dogs died within 72 hours after receiving a single oral dose of 4,180-12,540 mg/kg/day ethylene glycol (Kersting and Nielson 1965).

The oral dose of ethylene glycol required to cause death in humans is not well defined in the literature. However, the minimum lethal dose for adults is thought to be 1.4 mL/kg of 95% ethylene glycol, or about 1,330 mg ethylene glycovkg body weight (Parry and Wallach 1974; Robinson and McCoy 1989; Siew et al. 1975a).

The possibility exists for humans to accidentally ingest sufficient amounts of ethylene glycol in antifreeze to cause irreversible adverse effects or death. However, it is very unlikely that persons living in the vicinity of hazardous waste sites could ingest sufficient amounts of soil or water contaminated with ethylene glycol to cause death.

No studies were located regarding death in humans after oral exposure to propylene glycol.

Oral LD_{50} values have been reported in rats (range, 8-46 g/kg), mice (range, 25-32 g/kg), and guinea pigs (range, 18-20 g/kg) after acute oral exposure to propylene glycol (Clark et al. 1979; EPA 1987a; Ruddick 1972). Male Wistar rats (6/group) were orally dosed with saline or 2,942 mg/kg/day , propylene glycol in water for 10, 20, or 30 days (Morshed et al. 1991a). No death was observed. A fatal case of propylene glycol poisoning occurred in a horse given 3.8 L (7,904 mg/kg) of propylene glycol instead of mineral oil. The horse died of respiratory arrest 28 hours after administration (Dorman and Haschek 1991). It is unlikely that sufficient amounts of propylene glycol can be present or ingested near hazardous waste sites to cause death among people living in the area.

All reliable LOAEL and LD_{50} values for death in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3, and plotted in Figure 2-3. The LD_{50} value for death in rats after acute duration oral exposure to propylene glycol are reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, endocrine, hepatic, dermal, ocular, or body weight effects in humans, or ocular effects in animals after oral exposure to ethylene glycol. No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans, or musculoskeletal, dermal, or ocular effects in animals after oral exposure to propylene glycol.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and Figure 2-3. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-4 and Figure 2-4.

Respiratory Effects. Respiratory system involvement occurs 12-24 hours after ingestion of sufficient amounts of ethylene glycol and is considered to be a second stage in ethylene glycol poisoning (Vale 1979). The symptoms include hyperventilation (Godolphin et al. 1980; Gordon and Hunter 1982), shallow rapid breathing (Woolf et al. 1992; Zeiss et al. 1989), and generalized pulmonary edema with calcium oxalate crystals occasionally present in the lung parenchyma (Vale 1979). Respiratory failure was observed in a woman who had consumed 9,771 mg/kg ethylene glycol (as antifreeze) (Blakeley et al. 1993). It appears that respiratory system involvement is dose-dependent and occurs concomitantly with cardiovascular changes. Symptoms related to acidosis such as hyperpnea and tachypnea are frequently observed; however, major respiratory morbidities such as pulmonary edema rarely occur, having been reported in only 5 of 36 severely poisoned cases (Karlson-Stilber and Persson 1992).

Respiratory effects have been observed in dogs after oral exposure to ethylene glycol (Kersting and Nielson 1965). Congestion, edema, hyperpnea, and tachypnea were observed in dogs during the second or third hour after a single oral dose of up to 12,540 mg/kg. The doses at which the

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Human	once				7070 M (death 68 hours after ingestion of EG)	Gordon and Hunter 1982
2	Human	once				4071 M (death 48 hrs after ingestion)	Siew et al. 1975a
3	Human	once				2379 (death in 6/11)	Walton 1978
4	Rat (Fischer 344)	once (G)				4000 F (LD_{50})	Clark et al. 1979
5	Mouse (Swiss CD-1)	8 d Gd 7-14 1x/d (G)				11090 F (5/50 died)	Schuler et al. 1984
6	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)				2000 F (8/19 died)	Tyl et al. 1993
	Systemic						
7	Human	once	Metab			4332 M (severe metabolic acidosis)	Cheng et al. 1987
8	Human	once	Resp		7070 M (hyperventilation)		Gordon and Hunter 1982
			Cardio			7070 M (myocardial failure)	
			Renal			7070 M (renal failure)	
			Metab			7070 M (metabolic acidosis)	

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
9	Human	once	Renal			11238 F (calcium oxalate crystalluria)	Heckerling 1987
			Metab			11238 F (metabolic acidosis, increased bromide; ion gap)	
10	Human	once	Renal			2714 M (renal failure)	Mallya et al. 1986
11	Human	once	Cardio			3171 M (tachycardia, ventricular gallop)	Parry and Wallach 1974
			Renal			3171 M (calcium oxalate crystalluria, renal failure)	
			Metab			3171 M (metabolic acidosis)	
12	Human	once	Renal			7600 M (ethylene glycol in urine)	Peterson et al. 1981
			Metab			7600 M (ethylene glycol in blood; metabolic acidosis)	
13	Human	once	Cardio			4071 M (ventricular tachycardia, cardiac arrest)	Siew et al. 1975a
			Renal			4071 M (oxalate nephrosis)	
			Metab			4071 M (metabolic acidosis)	
14	Human	once (W)	Gastro			12839 M (upper gastrointestinal bleeding)	Spillane et al. 1991
			Renal			12839 M (increased creatinine, renal failure)	
			Metab			12839 M (metabolic acidosis, ion gap)	
15	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)	Bd Wt		2500 F (treatment period weight gain decreased 27%; gestational weight gain decreased 13%)		Marr et al. 1992

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
16	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)	Hepatic	2500 F			Neeper-Bradley 1990
			Renal	1000 F	2500 F (increased absolute and relative kidney weight)		
			Bd Wt	1000 F	2500 F (decreased body weight)		
17	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)	Renal	250		1250 (oxalate nephrosis, tubular dilatation and degeneration)	NTP 1988
			Bd Wt	2250			
18	Rat (CD)	10 d 1x/d (GW)	Hepatic	2500 F	5000 F (11% decreased liver weight in dams)		Price et al. 1985
			Body Wt		1250 F (17% decreased body weight)		
19	Mouse (B6C3F1)	4 d (GW)	Resp	1000			Hong et al. 1988
			Cardio	1000			
			Gastro	1000			
			Hemato	400 F	200 M (bone marrow 1000 F hypo-cellularity)		
			Hepatic	1000			
			Renal	1000			
20	Mouse (CD-1)	10 d 1x/d (GW)	Hepatic	750 F	1500 F (reduced liver weight in dams)		Price et al. 1985
			Body Wt	750 F	1500 F (31% reduced weight gain)		

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
21	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)	Hepatic	1500 F			Tyl 1989
			Renal	1500 F			
			Bd Wt	1500 F			
22	Dog	once (F)	Renal			10743 (renal failure, oxalate nephrosis)	Grauer et al. 1987
23	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)	Hepatic	2000 F			Tyl et al. 1993
			Renal			2000 F (intraluminal oxalate crystals, epithelial necrosis, and tubular dilatation and degeneration of the cortical tubules)	
			Bd Wt	2000 F			
24	Cat	once (G)	Renal			4440 (oxalate nephrosis)	Penumarthy and Oehme 1975
	Neurological						
25	Human	once				9771 F (unresponsive, incontinent, no corneal, gag, or deep-tendon reflexes)	Blakeley et al. 1993
26	Human	once				4332 M (tremors, agitation)	Cheng et al. 1987
27	Human	once			7070M (restlessness, violent behavior)		Gordon and Hunter 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Human	once				11238 F (unresponsive to deep pain, delayed pupillary light reflex, no deep tendon or corneal reflex)	Heckerling 1987
29	Human	once				2714 M (bilateral facial paralysis, hearing loss, absent gag reflex, unilateral facial numbness)	Mallya et al. 1986
30	Human	once				3171 M (ataxia, somnolence, slurred speech, stupor, seizures, bilateral 6th nerve paralysis, lethargy)	Parry and Wallach 1974
31	Human	once				4071 (stupor, loss of consciousness, coma)	Siew et al. 1975a
32	Human	once				12839 M (unresponsive, depressed mental status, dysfunction of cranial nerves 9 and 10)	Spillane et al. 1991
33	Dog	once (F)				10743 (depression, ataxia)	Grauer et al. 1987
34	Cat	once (G)				4440 (convulsions and coma)	Penumarthy and Oehme 1975
	Reproductive						
35	Rat (Fischer 344)	10 d Gd 6-15 (F)		1000 F			Maronpot et al. 1983

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
36	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)		2500			Neeper-Bradley 1990
37	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)		1250		2250 (decreased prenatal viability)	NTP 1988
38	Rat (CD)	10 d Gd 6-15 1x/d (GW)		2500		5000 F (postimplantation loss)	Price et al. 1985
39	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)				750 F (reduced litter size)	Price et al. 1985
40	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)		1500			Tyl 1989
41	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)		1000 F		2000 F (abortion or early delivery)	Tyl et al. 1993
	Developmental						
42	Rat (Fischer 344)	10 d Gd 6-15 (F)		1000 F			Maronpot et al. 1983

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
43	Rat (Sprague-Dawley)	10 d Gd 6-15 1x/d (GW)		500		1000 (increased skeletal malformations)	Neeper-Bradley 1990
44	Rat (Sprague-Dawley)	Gd 6-20 1x/d (GW)		1250		2250 (decreased prenatal and postnatal viability, increased malformations in the axial skeleton)	NTP 1988
45	Rat (CD)	10 d Gd 6-15 1x/d (GW)				1250 F (increased skeletal malformations in fetuses)	Price et al. 1985
46	Mouse (Swiss Crl:CD-1)	7 d Gd 8-14 1x/d (GW)		700	2500 (decreased pup body weight on ppd 1 and 4)		Harris et al. 1992
47	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)				750 F (increased skeletal malformations in fetuses)	Price et al. 1985
48	Mouse (CD-1)	10 d Gd 6-15 1x/d (GW)		150[b]		500 (increased total malformations and one skeletal variation: bilateral extra rib 14)	Tyl 1989
49	Rabbit (New Zealand)	14 d Gd 6-19 1x/d (GW)		2000 F			Tyl et al. 1993

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	INTERMEDIATE EXPOSURE						
	Death						
50	Rat (Fischer 344/N)	13 wk (F)				2500 M (death in 4/10 males)	Melnick 1984
	Systemic						
51	Rat (Fischer 344)	3 gen (F)	Renal	200	1000 (mild focal interstitial nephritis)		DePass et al. 1986b
			Bd Wt	1000			
52	Rat (Fischer 344/N)	13 wk (F)	Renal	625		1250 (oxalate nephrosis, renal failure)	Melnick 1984
			Bd Wt	625 M 2500 F	1250 M (10% decrease in body weight)		
53	Mouse (Swiss Crl:CD-1)	17 d 1x/d (GW)	Hepatic	2500 M			Harris et al. 1992
			Renal	2500 M			
			Bd Wt	2500 M			
54	Mouse (Swiss Crl:CD-1)	20 d 1x/d (GW)	Other	2500 F			Harris et al. 1992

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
55	Mouse (B6C3F1)	13 wk (F)	Hemato	6500			Melnick 1984
			Hepatic	1625 M 6500 F	3250 M (hyaline degeneration of centrilobular hepatocytes)		
			Renal	1625 M 6500 F	3250 M (mild nephrosis and regenerative hyperplasia)		
56	Mouse (JCL-ICR)	5 wk 5d/wk 1x/d (G)	Hemato	4000 M			Nagano et al. 1984
57	Mouse (B6C3F1)	13 wk 1x/d (F)	Hemato	6500			NTP 1992
			Hepatic	1625 M 6500 F	3250 M (hyaline degeneration of centrilobular hepatocytes)		
			Renal	1625	3250 (tubular dilation, vacuolation, degenerative hyperplasia)		
			Bd Wt	819 M 6500 F	1625 M (significantly lower body weight in males)		
	Neurological						
58	Rat (Fischer 344\N)	13 wk (F)		1250 M 2500 F		2500 M (calcium oxalate deposits in brain blood vessel walls)	Melnick 1984

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference
	Reproductive							
59	Rat (Fischer 344)	3 gen (F)		1000				DePass et al. 1986b
60	Mouse (Swiss Crl:CD-1)	17 d 1x/d (GW)		2500				Harris et al. 1992
61	Mouse (Swiss Crl:CD-1)	20 d 1x/d (GW)		700		2500	(decreased live fetuses, increased dead implants, 2/6 litters totally resorbed)	Harris et al. 1992
62	Mouse (JCL-ICR)	5 wk 5d/wk 1x/d (G)		4000M				Nagano et al. 1984
	CHRONIC EXPOSURE							
	Death							
63	Rat (Sprague-Dawley)	2 yr (F)				500 M	(16/16 died within 18 months)	Blood 1965
						2000 F	(16/16 died within 18 months)	
64	Rat (Fischer 344)	24 mo (F)				1000 M	(130/130 males died prior to month 16)	DePass et al. 1986a; Woodside et al. 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Systemic						
65	Rat (Fischer 344)	12 mo (F)	Resp	1000			DePass et al. 1986a; Woodside et al. 1982
			Gastro	1000			
			Hemato	200 M 1000 F	1000 M (decreased hematocrit, reduced RBC, reduced HGB, increased neutrophils)		
			Hepatic	200 F 1000 M	1000 F (fatty metamorphosis)		
			Renal	200 [c] M		1000 M (oxalate nephrosis in males; chronic nephritis)	
				200 F	1000 F (urinary oxalate)		
			Bd Wt	200 M 1000 F	1000 M (weight loss)		
66	Rat (Fischer 344)	24 mo (F)	Resp	200 M 1000 F			DePass et al. 1986a; Woodside et al. 1982
			Gastro	200 M 1000 F			
			Hemato	200 M 1000 F			
			Hepatic	200 M 200 F	1000 F (fatty metamorphosis)		
			Renal	40	200 (urinary oxalate)		

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
67	Mouse (Charles River CD-1)	12 mo (F)	Resp	1000			DePass et al. 1986a
			Cardio	1000			
			Gastro	1000			
			Musc/sk	1000			
			Hepatic	1000			
			Renal	1000			
			Endocr	1000			
			Dermal	1000			
68	Mouse (B6C3F1)	2 yrs 1x/d (F)	Resp	3250 F	6500 F (pulmonary arterial medial hyperplasia)		NTP 1992
			Hepatic	3250 F	6500 F (hyaline degeneration of centrilobular hepatocytes)		
			Bd Wt	6500 F			
69	Mouse (B6C3F1)	2 yr 1x/d (F)	Hepatic	812.5 M	1625 M (hyaline degeneration of centrilobular hepatocytes)		NTP 1992
			Renal	1625 M		3315 M (oxalate nephrosis, urethra oxalate deposits)	
	Immunological/Lymphoreticular						
70	Rat (Fischer)	24 mo contin-uous (F)		200	1000 (M: increased neutrophils; F: hemosiderosis in the lymph nodes)		DePass et al. 1986a; Woodside 1982

TABLE 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
71	Mouse (Charles River CD-1)	12 mo (F)		1000			DePass et al. 1986a
	Reproductive						
72	Rat (Fischer 344)	24 mo (F)		1000			DePass et al. 1986a; Woodside et al. 1982
73	Mouse (Charles River CD-1)	24 mo (F)		1000			DePass et al. 1986a

[a]The number corresponds to entries in Figure 2-3.

[b]Used to derive an acute oral minimal risk level (MRL) of 2.0 mg/kg/day; NOAEL divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability)

[c]Used to derive a chronic oral MRL of 2.0 mg/kg/day; NOAEL divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; gen = generation; (GW) = gavage in water; HGB = hemoglobin; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; ppd = post-parturition day; RBC = red blood cell; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral

Acute (≤14 days)

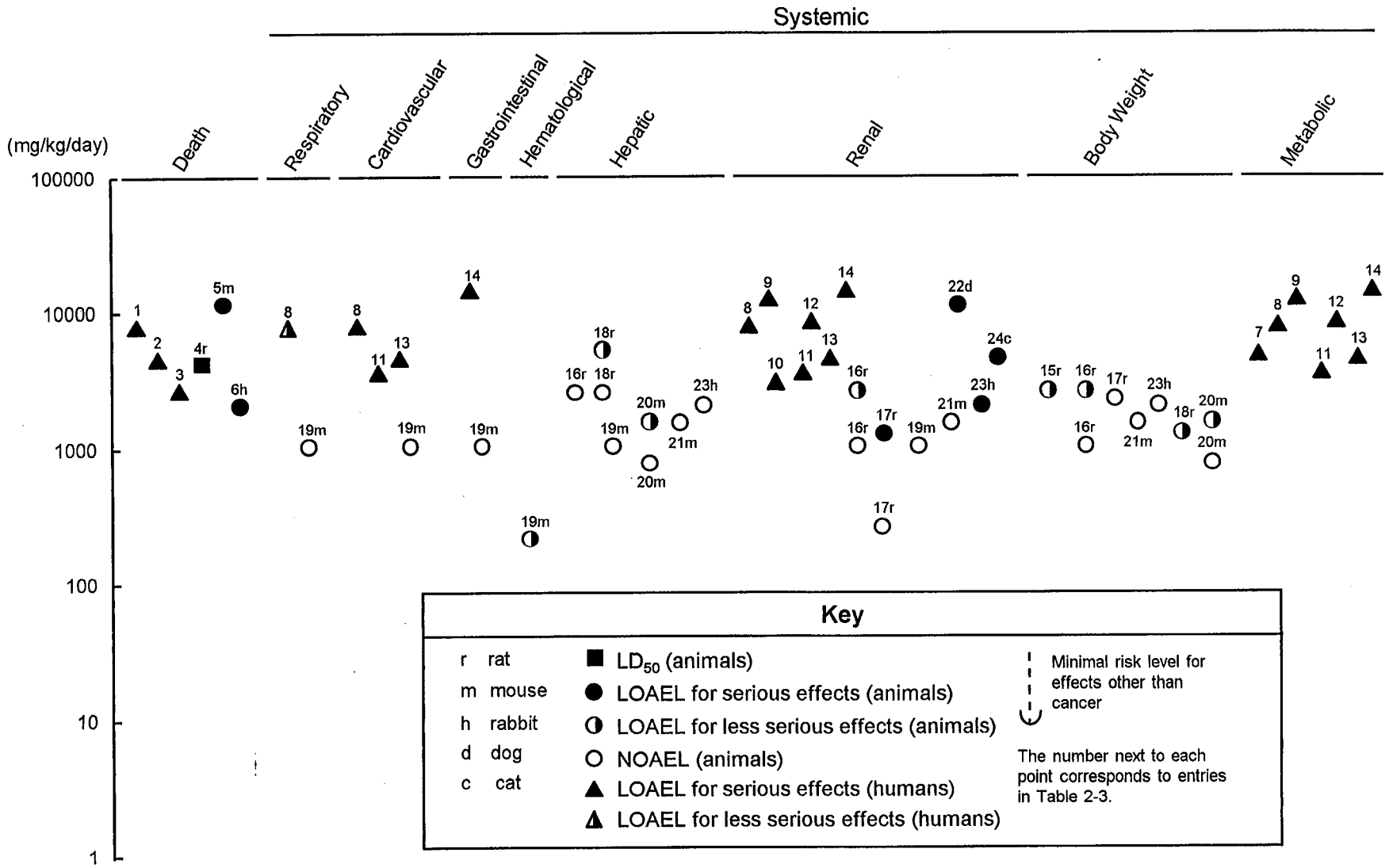


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Acute (≤14 days)

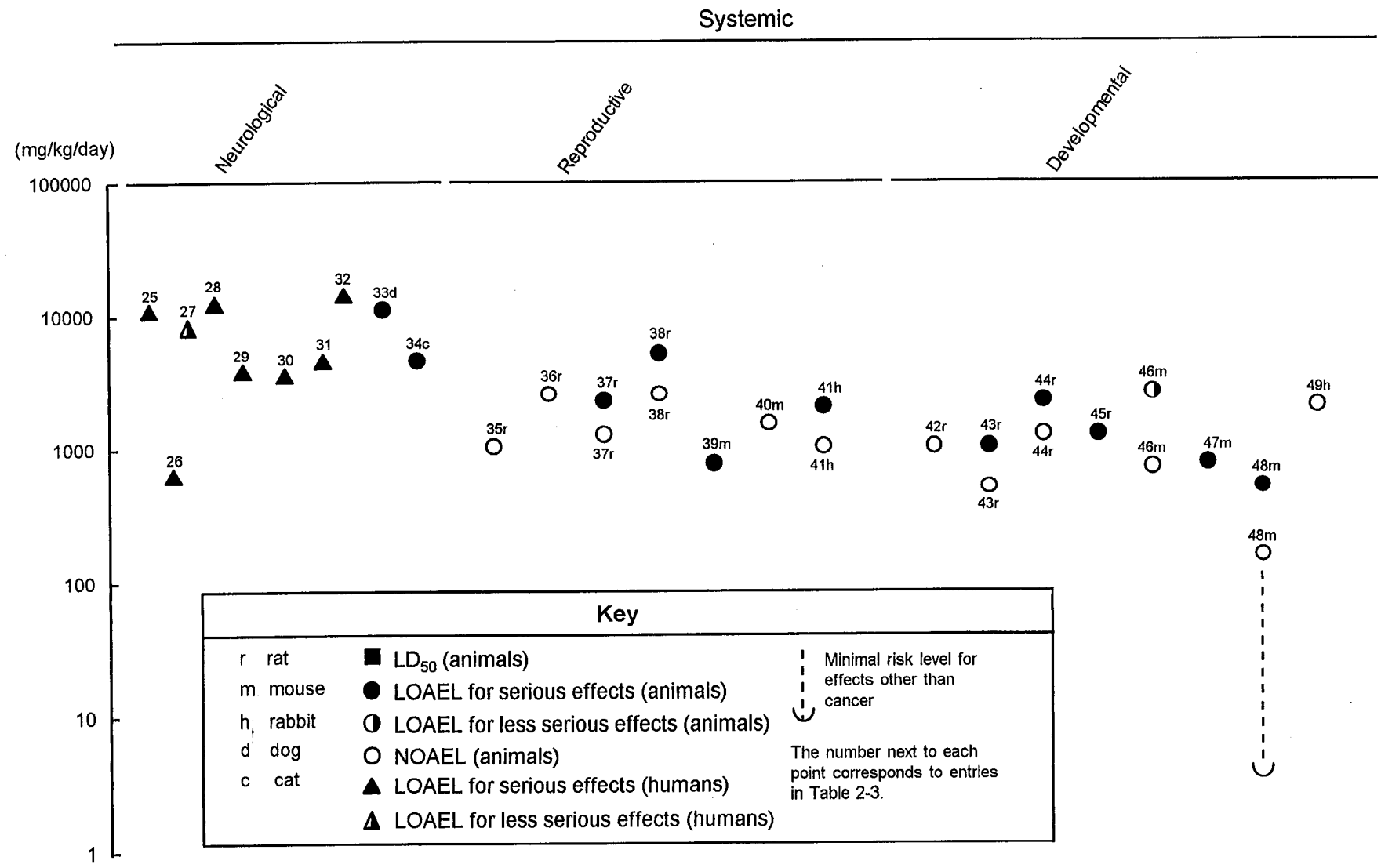


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Intermediate (15-364 days)

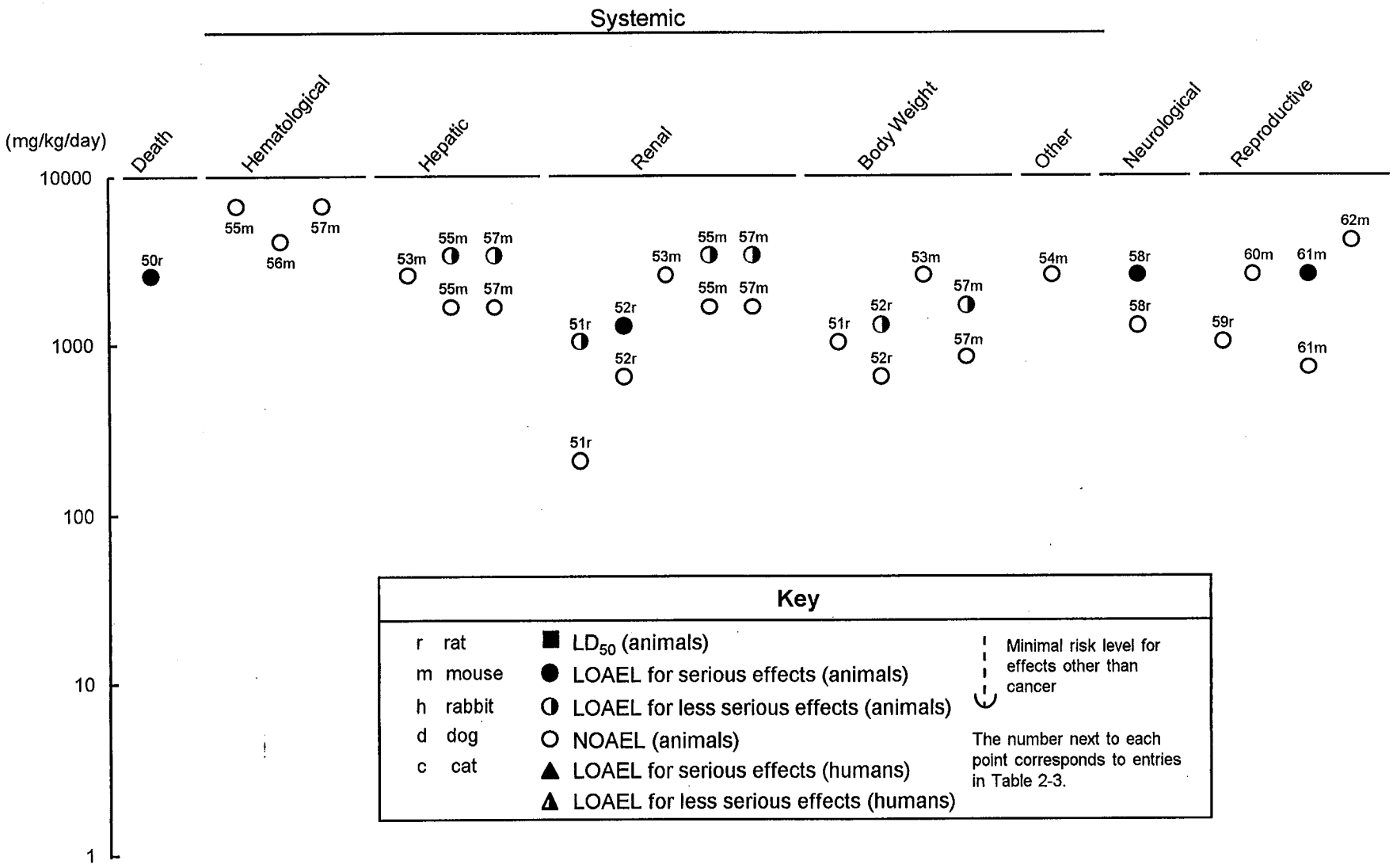


Figure 2-3. Levels of Significant Exposure to Ethylene Glycol - Oral (continued)

Chronic (≥365 days)

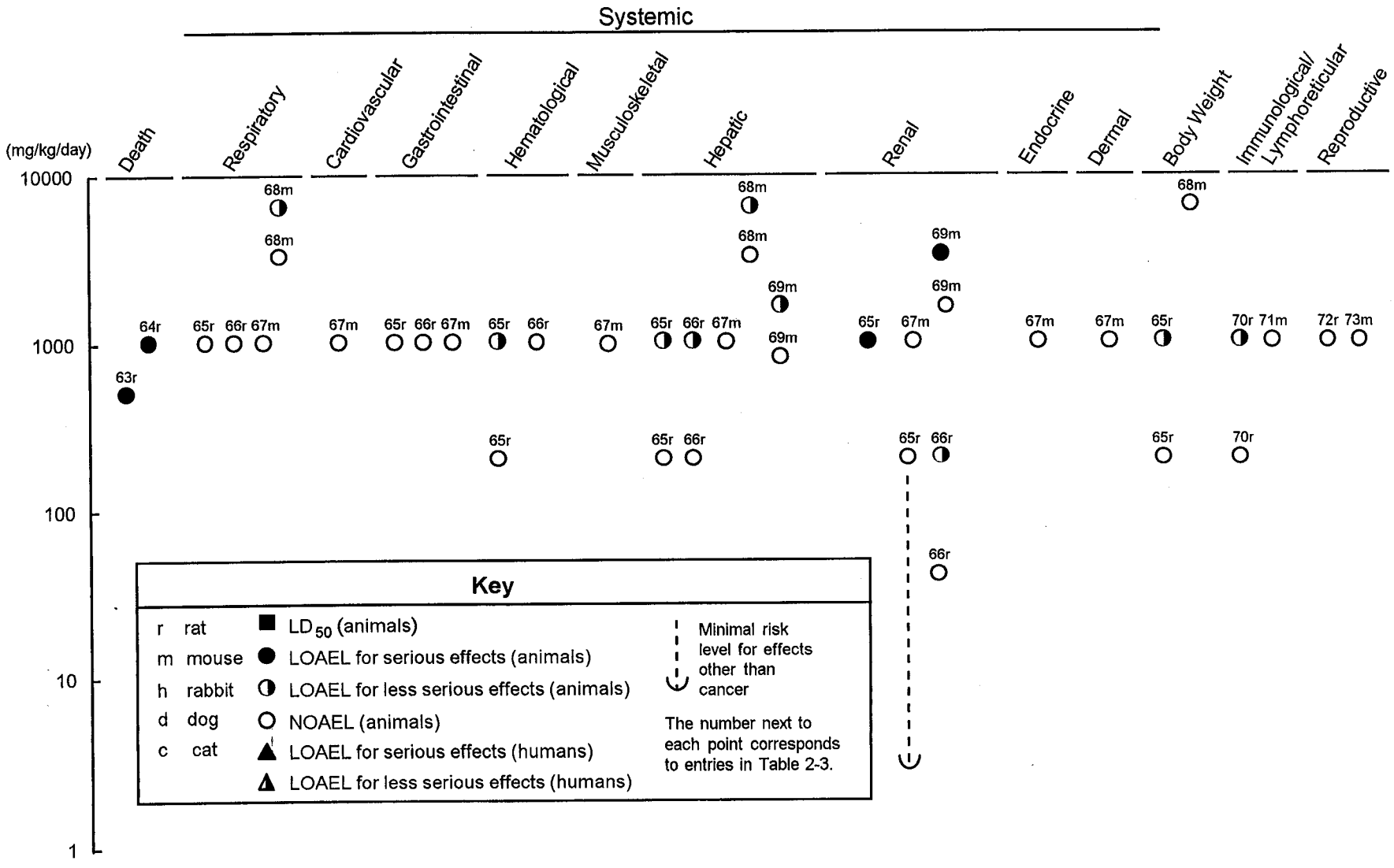


TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer 344)	once (G)				22800 F (LD_{50})	Clark et al. 1979
	Systemic						
2	Rat (Fischer 344)	once (G)	Gastro			23500 F (hemorrhagic enteritis)	Clark et al. 1979
			Hemato			23500 F (lymphocyte depletion)	
			Endocr			23500 F (adrenocortical hemorrhage)	
3	Cat (NS)	14 d (F)	Hemato		3600 (reticulocytosis, increased Heinz bodies, increased severe mechanical fragility)		Weiss et al. 1992
	Immunological/Lymphoreticular						
4	Cat (NS)	14 d (F)			3600 (decreased haptoglobin concentrations)		Weiss et al. 1992
	Neurological						
5	Rat (Fischer 344)	once (G)				22800 F (lethargy and coma)	Clark et al. 1979
	Reproductive						
6	Mouse (CD-1)	5 d 1x/d (GW)		10000			Kavlock et al. 1987

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Developmental						
7	Mouse (CD-1)	5 d 1x/d (GW)		10000			Kavlock et al. 1987
	INTERMEDIATE EXPOSURE						
	Systemic						
8	Cat	13 wk (F)	Hemato		1260 (increased Heinz bodies, decreased RBC survival)		Bauer et al. 1991
9	Cat	13 wk (F)	Hemato		2750 (increased Heinz bodies, increased punctate reticulocytes, decreased RBC survival)		Bauer et al. 1992
10	Cat	5 wk (F)	Hemato		1600 (Heinz body formation)		Christopher et al. 1989a
			Renal	1600			
11	Cat	3 wk (F)	Hemato			8000 (hypercellularity)	Christopher et al. 1989a
			Renal		8000 (polyuria, polydipsia)		
12	Cat Mongrel	22-35 d (F)	Renal	1600	8000 (polyuria, polydipsia)		Christopher et al. 1990b
			Metab		1600 (increased anion gap, increased D-lactate)		
13	Cat	17 wk (F)	Hemato		2400 (Heinz body formation)		Weiss et al. 1990

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	Neurological						
14	Cat Mongrel	22-35 d (F)		1600		8000 (ataxia, CNS depression, decreased activity)	Christopher et al. 1990b
	Reproductive						
15	Mouse (Swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	Developmental						
16	Mouse (Swiss CD-1)	15-18 wk daily (W)		10118			NTP 1985
	CHRONIC EXPOSURE						
	Systemic						
17	Rat	2 yr (F)	Resp	2500			Gaunt et al. 1972
			Cardio	2500			
			Hemato	2500			
			Hepatic	2500			
			Renal	2500			
			Endocr	2500			
18	Dog	2 yr (F)	Hemato	2000	5000 (decreased erythrocytes, hemoglobin, hematocrit)		Weil et al. 1971
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			

TABLE 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Immunological/Lymphoreticular						
19	Dog	2 yr (F)		5000			Weil et al. 1971

[a]The number corresponds to entries in Figure 2-4.

Bd Wt = body weight; Cardio = cardiovascular; CNS = central nervous sytem; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; RBC = red blood cell; (W) = gavage in water; wk = week(s); x = times; yr = year(s)

Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral

Acute (≤14 days)

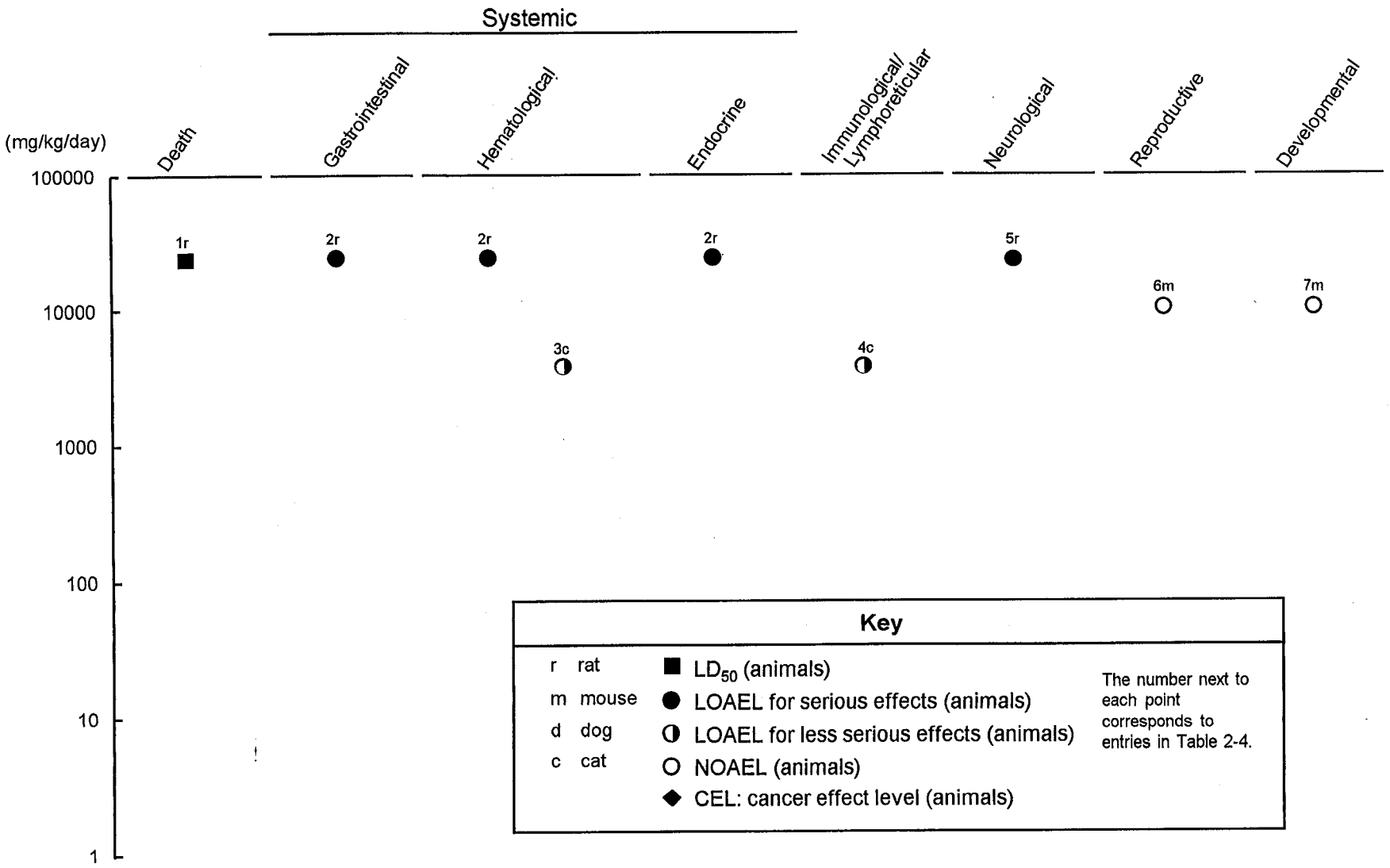


Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)

Intermediate (15-364 days)

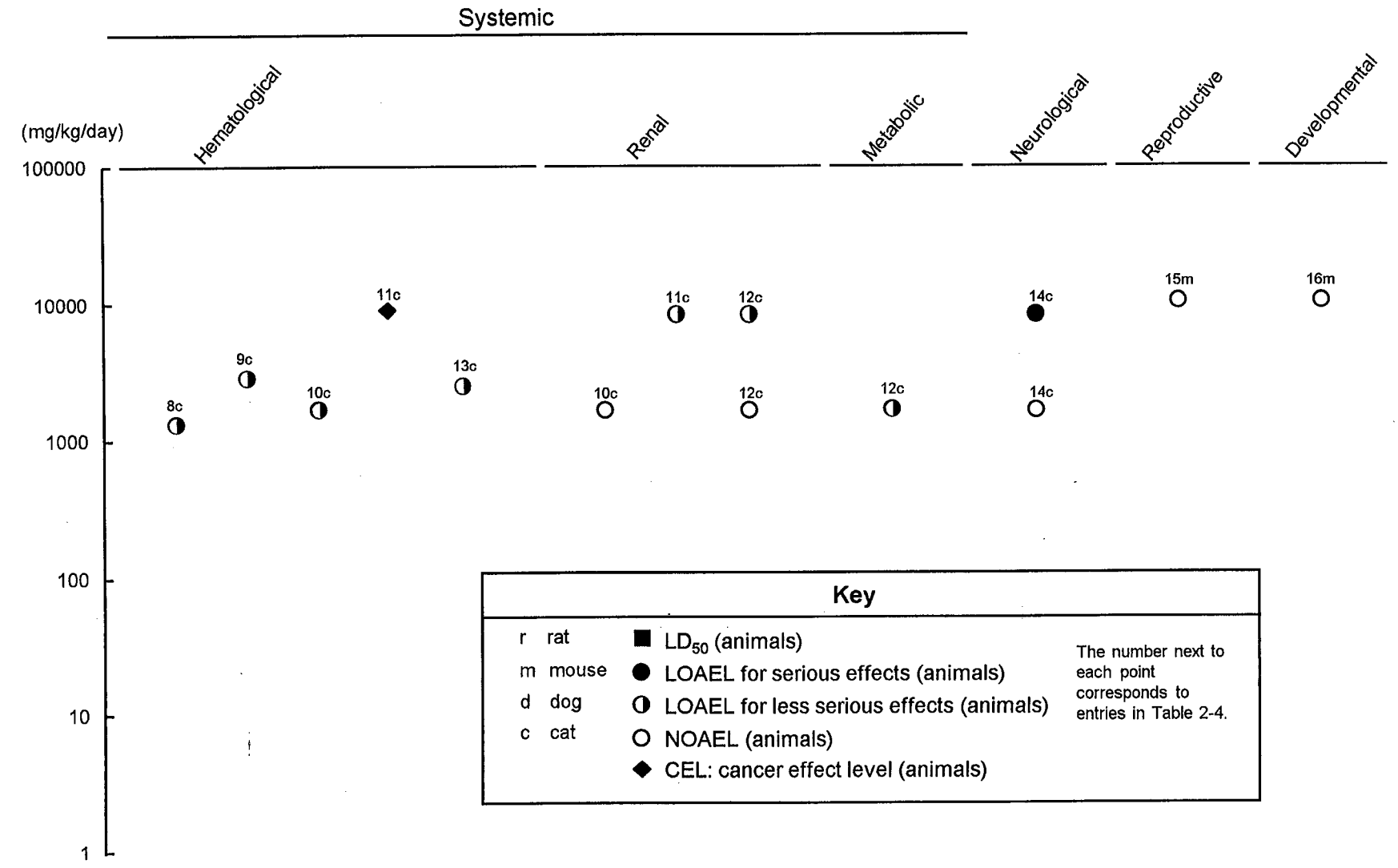
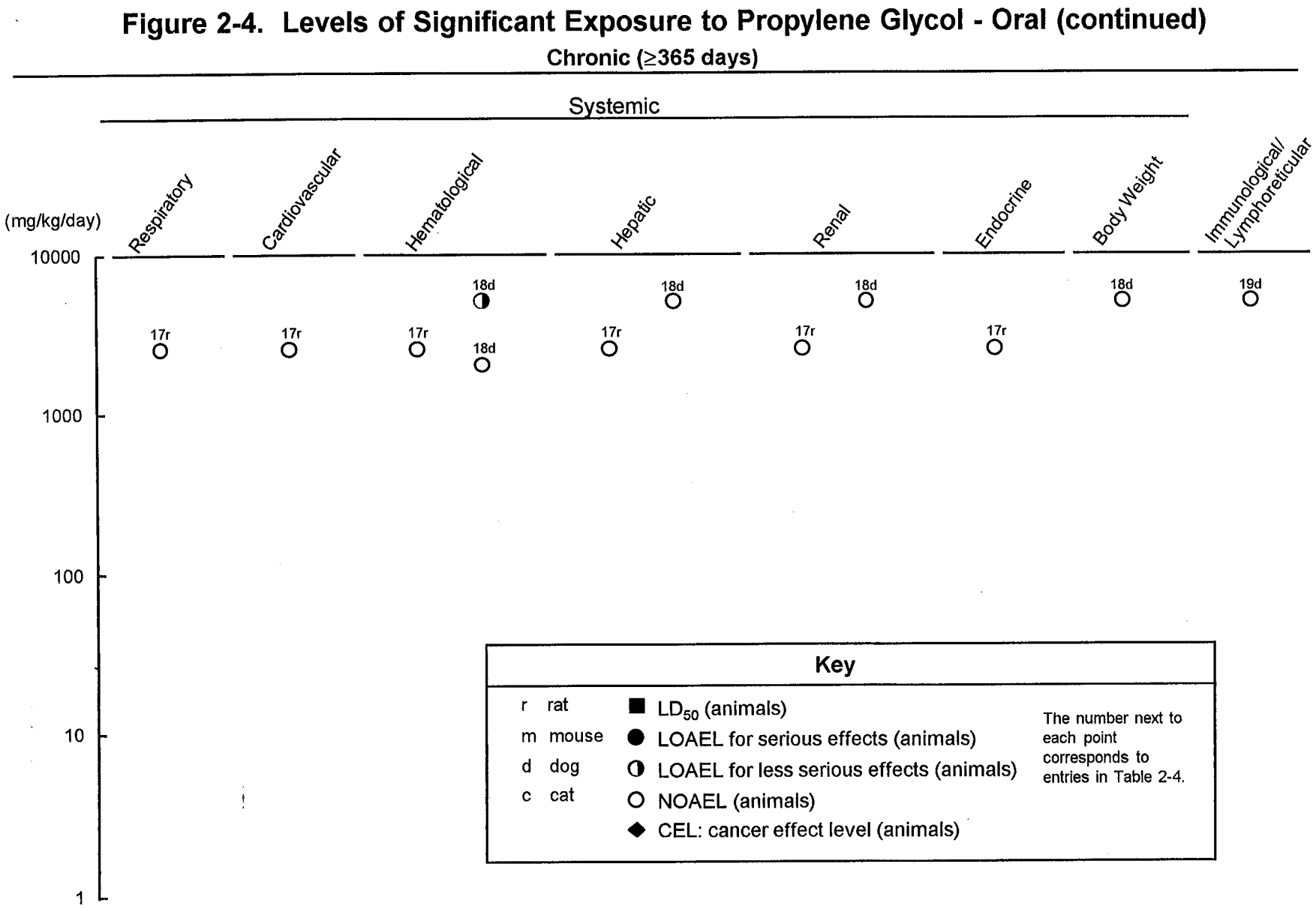


Figure 2-4. Levels of Significant Exposure to Propylene Glycol - Oral (continued)



respiratory effects were seen were not specified. General mineralization of soft tissues, including pulmonary tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

In rats there were no changes in any of the respiratory parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972).

Cardiovascular Effects. Cardiovascular system involvement in humans occurs at the same time as respiratory system involvement, during the second phase of oral ethylene glycol goisoning, which is 12-24 hours after acute exposure (Vale 1979). The symptoms of cardiac involvement include tachycardia, ventricular gallop (Parry and Wallach 1974; Siew et al. 1975a), and cardiac dilatation (Vale 1979). Repeated cardiac arrhythmias were observed prior to cardiac arrest and death in a 22-year-old man who ingested 4,071 mg/kg of ethylene glycol (Siew et al. 1975a). Episodes of hypotension were also observed prior to renal failure and death in a 73-year-old man who ingested 7,850 mg/kg ethylene glycol, contained in antifreeze (Gordon and Hunter 1982). As in the case of respiratory effects, cardiovascular involvement occurs with ingestion of relatively high doses of ethylene glycol. Nevertheless, circulatory disturbances are a rare occurrence, having been reported in only 8 of 36 severely poisoned cases (Karlson-Stilber and Persson 1992). Therefore, it appears that acute exposure to high levels of ethylene glycol can cause serious cardiovascular effects; however, it is unlikely that such levels would be found in water close to hazardous waste sites and consumed by those living in the vicinity. The effects of a long-term, low-dose exposure are unknown.

In dogs, bradycardia and hemorrhages of the myocardium were found in those fatally exposed to an acute oral dose of ethylene glycol (Kersting and Nielson 1965). General mineralization of soft tissues, including cardiac tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

The heart histopathology of rats after a 2-year oral exposure to 2,500 mg/kg/day of propylene glycol revealed no changes (Gaunt et al. 1972). A similar lack of cardiovascular effects was observed in rats by Morris et al. (1942) after a 23-month exposure to 49,500 mg/kg/day propylene glycol in the feed.

A horse developed myocardial edema prior to death caused by accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

Gastrointestinal Effects. A 33-year-old man who drank a quart of ethylene glycol (12,840 mg/kg) developed upper gastrointestinal tract bleeding secondary to multiple gastric lesions (Spillane et al. 1991). It is not clear whether or not the gastric lesions were a pre-existing condition in this patient.

General mineralization of soft tissues, including stomach tissue, was noted in male Fischer 344 rats after a l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). This effect may be the result of altered calcium metabolism as a result of ethylene glycol exposure (Rajagoopal et al. 1977).

Fischer 344 rats exhibited hemorrhagic enteritis after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for 10-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected.

Hematological Effects. The hematological parameters-white blood cells, red blood cells, hematocrit, and hemoglobin-were not affected in mice after acute oral ethylene glycol-treatment, but hypocellularity and suppression of colony-forming units were quite evident at a dose of 1,000 mg/kg/day (Hong et al. 1988). Male mice treated orally with doses of ethylene glycol up to 4,000 mg/kg/day for 5 weeks showed no adverse hematological effects (Nagano et al. 1984). Male Fischer 344 rats treated with 1,000 mg/kg/day of ethylene glycol orally for 2 years had a reduced erythrocyte count, reduced hematocrit, and reduced hemoglobin (DePass et al. 1986a; Woodside 1982).

In another study, male and female Sprague-Dawley rats fed ethylene glycol at doses up to 2,000 mg/kg/day for 2 years showed no significant hematologic effects (Blood 1965).

Because of the availability of ethylene glycol, ingestion of high doses can occur and lead to adverse blood chemistry changes. However, such effects are unlikely to occur in populations living near hazardous waste sites since the ethylene glycol concentration necessary to cause such adverse effects is relatively high.

Limited information was available on hematological effects of propylene glycol in humans after oral exposure. A 39-year-old woman who had ingested propylene glycol and ethanol showed no adverse effects on blood chemistry (Lolin et al. 1988).

The results from animal studies indicate that intermediate and chronic exposure to propylene glycol may lead to hemolysis of red blood cells. Increased numbers of Heinz bodies (sign of red blood cell degeneration) were observed in cats exposed orally to 1,200, 1,600, 2,400, and 3,600 mg/kg of propylene glycol for 2, 5, and 17 weeks, respectively (Christopher et al. 1989a; Weiss et al. 1990, 1992). Other studies indicate increased Heinz body formation and decreased RBC survival in kittens and adult cats ingesting 3,000 mg/kg and 1,400 mg/kg/day, respectively (Bauer et al. 1992). These findings are further supported by results obtained in dogs after chronic oral exposure to 5,000 mg/kg/day (Weil et al. 1971). Red blood cell hemolysis was evidenced by decreased hemoglobin and hematocrit levels, and decreased total red blood cell counts. In rats, however, there were no changes in any of the hematological parameters after 2 years of chronic oral exposure to 2,500 mg/kg/day propylene glycol (Gaunt et al. 1972). These results indicate that there may be species differences with regard to the effect of propylene glycol on red blood cells. Fischer 344 rats exhibited lymphocyte depletion after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). Hypocellularity of the bone marrow was observed in cats after intermediate oral exposure to 8,000 mg/kg/day of propylene glycol (Christopher et al. 1989a).

Musculoskeletal Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal musculoskeletal effects (DePass et al. 1986a).

Hepatic Effects. In mice exposed to an oral dose of 1,000 mgkg of ethylene glycol, histopathology did not reveal any liver changes 1, 5, or 14 days after treatment (Hong et al. 1988).

Neither was there any effect in male mice after 17 days of oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Similarly, Fischer 344 rats fed up to 2,500 mg/kg/day ethylene glycol for 13 weeks showed no treatment-related effect on the liver (Melnick 1984). Male mice fed doses of ethylene glycol up to 6,500 mg/kg/day for 13 weeks exhibited degeneration of the centrilobular hepatocytes at doses ≥3,250 mg/kg/day (Melnick 1984; NTP 1992). Pregnant female Sprague-Dawley rats exhibited an 11% decrease in liver weight after oral dosing with 5,000 mg/kg/day ethylene glycol on Gd 6-15 (Price et al. 1985). However, pregnant CD rats and CD-l mice dosed with up to 2,500 mg/kg/day or 1,500 mg/kg/day ethylene glycol, respectively, using the same regimen, showed no hepatic effects (Neeper-Bradley 1990; Tyl 1989). Similarly, New Zealand White rabbits showed no hepatic effects after oral exposure to 2,000 mg/kg/day ethylene glycol on Gd 6-19 (Tyl et al. 1993). Fatty change of the liver was seen in female Fischer 344 rats fed 1,000 mg/kg/day of ethylene glycol for 2 years (DePass et al. 1986a; Woodside 1982). Ethylene glycol is absorbed relatively quickly after ingestion and evenly distributed throughout the body, while the liver is the main site of its oxidative degradation. The impact on liver function after short-term exposure to ethylene glycol appears to be quite minor.

The results from chronic-duration animal studies show that there are no adverse hepatic effects in rats fed a diet delivering 2,500 mg/kg/day of propylene glycol for 2 years (Gaunt et al. 1972). Based on these findings, it can be assumed that chronic oral exposures to moderately high levels of propylene glycol will not have adverse hepatic effects in humans. It is not clear if hepatotoxicity would result after an acute exposure to a high level of propylene glycol. Since levels of propylene glycol in the vicinity of a hazardous waste site would probably be low, it is unlikely that propylene glycol would induce adverse hepatic effects would occur in people living in the area.

Renal Effects. Adverse renal effects after ethylene glycol ingestion in humans can be observed during the third stage of ethylene glycol toxicity 24-72 hours after acute exposure. The hallmark of renal toxicity is the presence of birefringent calcium oxalate monohydrate crystals deposited in renal tubules and their presence in urine after ingestion of relatively high amounts of ethylene.glycol (Anonymous 1987; Blakeley et al. 1993; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al. 1975a; Underwood and Bennett 1973). In addition to birefringent oxalate crystals in the tubular lumens, other signs of nephrotoxicity can include focal tubular cell degeneration, atrophy, and tubular interstitial inflammation (Factor and Lava 1987). In a case study of a 3%year-old female who consumed 240 mL

of antifreeze (3,454 mg ethylene glycol/kg/day), crystalluria was not present upon hospital admission (about 12 hours after ingestion). Within 5 hours, excretion of calcium oxalate dihydrate crystals was evident, although monohydrate crystals became the primary form in the urine thereafter (2-3 hours) (Jacobsen et al. 1988). The presence of ethylene glycol metabolites-oxalic and glycolic acids-also contributes to nephrotoxicity. In the course of ethylene glycol intoxication, serum creatinine (Factor and Lava 1987; Spillane et al. 1991) and serum blood urea nitrogen (BUN) (Chung and Tuso 1989; Factor and Lava 1987) levels may be increased. If untreated, the degree of renal damage caused by high doses of ethylene glycol progresses and leads to hematmia (Anonymous 1987; Rothman et al. 1986; Underwood and Bennett 1973), proteinuria (Rothman et al. 1986), decreased renal function, oliguria, anuria (Mallya et al. 1986; Parry and Wallach 1974; Spillane et al. 1991; Woolf et al. 1992; Zeiss et al. 1989), and ultimately renal failure (Chung and Tuso 1989; Gordon and Hunter 1982; Jacobson et al. 1984; Mallya et al. 1986). These changes in the kidney are linked to acute tubular necrosis (Factor and Lava 1987), but normal or near normal renal function can return with adequate supportive therapy (Parry and Wallach 1974). In the majority of cases, the most effective therapy consists of hemodialysis and administration of ethanol as a substrate competitor of ethylene glycol for oxidative enzymes, leading to a decrease in the formation of toxic metabolites. Successful treatment of ethylene glycol poisoning has also been accomplished using 4-methyl pyrazole as a competitive substrate (Baud et al. 1987, 1988).

Rats receiving 1,400 mg/kg/day ethylene glycol in the drinking water for 3-29 days exhibited renal tubular oxalate deposits and/or crystalluria (Ebisuno et al. 1987; Khan et al. 1993), whereas in another study, enlarged kidneys were observed in Porton rats after 21 days of treatment with 999-1,110 mg/kg ethylene glycol in the drinking water (Rofe et al. 1986). No histopathological changes were observed in kidneys of mice after oral exposure to 1,000 mg/kg of ethylene glycol for up to 14 days (Hong et al. 1988). Neither was there any effect in male mice after 17 days oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Renal damage leading to oliguria and renal failure occurred in dogs (Beckett and Shields 1971; Grauer et al. 1987) and cats (Penumarthy and Oehme 1975) after a single oral exposure to 4,880 or 10,743 mg/kg (dogs) and 4,440 mg/kg of ethylene glycol (cats). Dogs receiving a single dose of 10,600 mg/kg ethylene glycol as antifreeze or as reagent grade ethylene glycol in feed exhibited polyuria and azotemia, and renal failure (Dial et al. 1994). In dogs given a dose of 1,000-l ,360 mg/kg/day, there were no increases in serum BUN or creatinine, suggesting normal renal function (Hewlett et al. 1989). In monkeys receiving ethylene glycol in drinking water

(0.25-10% for 6-13 days), 5 of 7 animals given doses greater than 1,388 mg/kg/day had calcium oxalate crystals and evidence of necrosis in the kidney (Roberts and Siebold 1969).

Pregnant mice exposed orally to 1,500 mg/kg/day ethylene glycol during gestation exhibited no renal effects (Tyl 1989); rats exposed to 2,500 mg/kg/day during gestation exhibited increased relative kidney weight but no adverse histopathological changes (Neeper-Bradley 1990). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Treatment-related renal pathology was evident in the mid- and high-dose dams. In contrast, New Zealand White rabbits given 2,000 mg/kg/day ethylene glycol by gavage during gestation exhibited characteristic renal toxicity including oxalate crystals, epithelial and tubular necrosis, and degeneration of the cortical tubules (Tyl et al. 1993). Fischer 344 rats receiving up to 2,500 mg/kg/day ethylene glycol in the feed for 13 weeks exhibited oxalate nephrosis and renal failure at doses of 1,250 mg/kg/day and above (Melnick 1984). Mice treated under the same regimen exhibited mild nephrosis at 3,250 mg/kg/day, and regenerative hyperplasia of the tubular epithelium (Melnick 1984). After a l-year exposure, male Fischer 344 rats, exhibited oxalate nephrosis and nephritis at 1,000 mg/kg/day in the feed (DePass et al. 1986a; Woodside 1982); male mice and rats exhibited the same effects after exposure to 3,315 mg/kg/day ethylene glycol in the feed for 2 years (NTP 1992). These findings indicate that there may be dose-response differences in the renal effects of ethylene glycol exposure. The results also show that the relationship between oxalate crystals in the kidney and nephrotoxicity is not causal, although the formation of oxalate crystals greatly contributes to renal toxicity. It seems reasonable to conclude from these studies that acute human exposure to relatively high doses of ethylene glycol leads to renal toxicity, but that chronic exposure to the low levels typically found in the vicinity of hazardous waste sites poses little risk of renal toxicity.

No adverse renal effects were observed in cats fed a diet delivering a dose of 1,600 mg/kg/day of propylene glycol for 5 weeks (Christopher et al. 1989a). In the same study, however, cats exposed to 8,000 mg/kg/day of propylene glycol for 3 weeks developed polyuria, considered a less serious adverse effect. In another study, an equal number (5-6) of cats of both sexes w.ere fed 1,600 mg/kg/day propylene glycol for 5 weeks or a high dose diet containing 8,000 mg/kg/day for 22 days (Christopher et al. 1990b). Cats fed the low dose had no adverse clinical signs. Cats fed the high dose had moderate polyuria and polydipsia. Chronic exposure of both rats and dogs to 2,500 and 5,000 mg/kg/day, respectively, for 2 years, had no nephrotoxic effects in either species (Gaunt et al. 1972; Weil et al. 1971). These results indicate that exposure to low levels of propylene glycol that

may be present at hazardous waste sites are not likely to cause adverse renal effects in the human population living in the vicinity.

Endocrine Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal histopathology of the endocrine organs (DePass et al. 1986a).

Fischer 344 rats exhibited adrenocortical hemorrhage after a single oral dose of 23,500 mg/kg propylene glycol (Clark et al. 1979). However, no adverse effects on endocrine organs were noted in rats exposed to 2,500 mg/kg/day ethylene glycol for 2 years (Gaunt et al. 1972).

Dermal Effects. CD-l mice fed up to 1,000 mg/kg/day ethylene glycol for 24 months showed no abnormal dermal effects (DePass et al. 1986a).

Body Weight Effects. Pregnant CD rats and CD-l mice showed a decrease in body weight after oral exposure to doses 11,250 or 1,500 mg/kg/day on Gd 6-15 (Marr et al. 1992; Neeper-Bradley 1990; Price et al. 1985). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). The high dose caused a significant decrease in dam weight on Gd 20 which was secondary to increased in utero death and which was not evident after delivery of the litter. However, in other studies, pregnant CD-l mice and New Zealand White rabbits showed no changes in body weight after oral exposure to 1,500 or 2,000 mg/kg/day ethylene glycol, respectively, on Gd 6-15 or 6-19 (Tyl 1989). There was no effect in male mice after 17 days oral treatment with 2,500 mg/kg/day (Harris et al. 1992). Male Fischer 344 rats showed a 10% decrease in body weight gain after exposure to 1,250 mg/kg/day ethylene glycol in the feed for 13 weeks (Melnick 1984), whereas male mice showed similar effects after exposure to 1,625 mg/kg/day via the diet (NTP 1992). In a 3-generation reproductive study, Fischer 344 rats showed no adverse effects on body weight after exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986b). After 1 year of exposure to 1,000 mg/kg/day ethylene glycol in the feed, male rats exhibited decreased body weight, but female rats did not (DePass et al. 1986a; Woodside 1982). CD-l micedid not exhibit any significant change in body weight after 24 months exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a).

Rats given 2,942 mg/kg propylene glycol by gavage for 10 days exhibited a 41% reduction in body weight, whereas exposure for 20-30 days caused an increase body weight (Morshed et al. 1991a).

Dogs exposed to 5,000 mg/kg/day oral propylene glycol for 2 years showed no adverse effect on body weight (Weil et al. 1971).

Metabolic Effects. One of the major adverse effects following acute oral exposure of humans to ethylene glycol involves metabolic changes. These changes occur as early as 12 hours after ethylene glycol exposure. Ethylene glycol intoxication at doses of 1,628 mg/kg/day is accompanied by metabolic acidosis which is manifested by decreased pH and bicarbonate content of serum and other bodily fluids caused by accumulation of excess glycolic acid (Anonymous 1987; Berger and Ayzar 1981; Blakeley et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Gordon and Hunter 1982; Heckerling 1987; Jacobsen et al. 1988; Parry and Wallach 1974; Siew et al. 1975a, Spillane et al. 1991; Woolf et al. 1992; Zeiss et al. 1989). There is an inverse relationship between the decreasing plasma pH and increasing plasma glycolic acid concentrations (Clay and Murphy 1977). The normal level of bicarbonate of 24 mmovL can be depleted in cases of severe ethylene glycol intoxication to reach concentrations as low as 2 mmol/L (Jacobsen et al. 1984). This decrease in base concentration indicates that a similar quantity of acid has to be present to achieve such a depletion. Glycolic acid is the only acidic metabolite present in such quantities. Humans highly intoxicated with ethylene glycol had glycolate concentrations from 17 to 29 mm01 and <l mmo1 of glyoxalate and oxalate (Jacobsen et al. 1984). Similar observations were made in animals. Metabolic acidosis due to glycolate accumulation was observed after acute oral exposure of dogs to 1,000-1,360 mg/kg of ethylene glycol (Hewlett et al. 1989), and of rats to 1,000 mg/kg (Marshall 1982). These results indicate that glycolic acid is the major toxic metabolite causing metabolic acidosis, and that its high serum levels are likely responsible for systemic toxicity observed after ethylene glycol exposure.

Other characteristic metabolic effects of ethylene glycol poisoning are increased serum anion gap, increased osmolal gap, and hypocalcemia. Serum anion gap is calculated from concentrations of sodium, chloride, and bicarbonate and is elevated after ethylene glycol ingestion (Chung and Tuso 1989; Factor and Lava 1987; Heckerling 1987; Spillane et al. 1991; Zeiss et al. 1989). The increase in the anion gap correlates with the elevation in plasma glycolate levels (Jacobsen et al. 1984). Osmolal gap represents the difference between the measured and calculated osmolalities and is also elevated during ethylene glycol intoxication. The amount of ethylene glycol causing these effects ranged from 1,628 to 12,840 mg/kg/day (Chung and Tuso 1989; Heckerling 1987; Spillane et al. 1991). The normal value for osmolal gap in humans is less than 10 (Fligner et al. 1985). Hypocalcemia occurs when oxalate chelates with calcium ions forming insoluble calcium oxalate monohydrate crystals. This

affects the overall ion concentration and can lead to an imbalance of divalent ion concentrations (Zeiss et al. 1989). Dogs receiving a single dose of 10,600 mg/kg ethylene glycol as antifreeze or as reagent grade ethylene glycol in feed exhibited metabolic acidosis and hyperosmolality (Dial et al. 1994).

High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. In a case of acute propylene glycol poisoning (the amount ingested not specified), the patient developed metabolic acidosis (pH of 7.29) with an osmolal gap of 51 mmol/kg (reference concentration is <l0 mmol/kg) (Lolin et al. 1988). There is a possibility that this patient also ingested a large amount of ethanol since the serum ethanol level was 90 mg/dL. The level of propylene glycol was 400 mg/dL in the serum and 10 mg/dL in urine.

Rats given oral doses of propylene glycol up to 5,885 mg/kg showed an increase of blood lactate of 2.7 mmol/L, which was prevented by inhibition of propylene glycol metabolism (Morshed et al. 1989). Rabbits given an oral dose of 2,942 mg/kg showed a similar increase in blood lactate of 2.6 mmol/L (Morshed et al. 1991b). In neither study was there a decrease in blood pH, probably because lactic acidosis in clinical situations occurs only when lactate levels rise more than 5 mmol/L (Morshed et al. 1989). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high-dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. In the low dose cats, anion gap increased from 15.5 Meq/liter during the control period to 22.2 Meq/liter on day 24 of exposure. Total CO_2, decreased at the end of the dosing period. Plasma D-lactate increased 24-fold during the dosing period and was significantly correlated with anion gap. L-lactate decreased significantly but in a less dramatic fashion to 31% of control values. Serum sodium increased slightly with dosing, but there were no other notable changes in serum chemistry. In high-dose cats, plasma D-lactate increased rapidly (44-fold) during dosing.

Other Systemic Effects. In a single mating reproductive trial, female CD-l mice were orally exposed to 250-2,500 mg/kg/day ethylene glycol for 20 consecutive days (Harris et al. 1992). The female mice showed no treatment-related clinical signs.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located specifically regarding immunological effects in humans or animals after oral exposure to ethylene glycol. Conflicting data were found regarding white blood cell counts, which were normal (Underwood and Bennett 1973) or elevated (Spillane et al. 1991) in two cases of oral ethylene glycol intoxication in humans.

Similar observations were made in mice after acute oral exposure to ethylene glycol at 1,000 mg/kg (Hong et al. 1988). An increased neutrophil count was present in male but not female Fischer 344 rats orally exposed to 1,000 mg/kg/day ethylene glycol in the feed for 12 months (DePass et al. 1986a; Woodside 1982). In the same study, increased neutrophil count was not seen in female Fischer 344 rats orally exposed to 1,000 mg/kg/day of ethylene glycol for 2 years, or in male rats exposed to 200 mg/kg/day ethylene glycol for 2 years (DePass et al. 1986a; Woodside 1982). No effect on neutrophil count was observed in CD-l mice exposed to 1,000 mgkglday ethylene glycol in the feed for 12 months (DePass et al. 1986a). Currently, there is no evidence that acute oral exposure to high concentrations of ethylene glycol adversely affects immunological functions. Intermediate oral exposure to low concentrations of ethylene glycol that may be present in the vicinity of hazardous waste sites is not likely to produce adverse immunological effects in populations residing in the area.

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to propylene glycol.

Cats fed 1.2 mg propylene glycol per gram of feed for 14 days showed increased haptoglobin concentration (Weiss et al. 1992). Dogs fed 5,000 mgkg/day propylene glycol for 2 years showed no adverse immunological effects (Weil et al. 1971).

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in rats after intermediate-duration oral exposure to ethylene glycol are reported inTable 2-3 and plotted in Figure 2-3. The highest NOAEL value and the LOAEL value for immunological and lymphoreticular effects in dogs and cats for each duration category for propylene glycol after oral exposure are reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.4 Neurological Effects

Adverse neurological reactions are among the first symptoms to appear in humans after ethylene glycol ingestion. These early neurotoxic effects are also the only symptoms attributed directly to ethylene glycol. Together with metabolic changes, they occur during the period of 30 minutes to 12 hours after exposure and are considered to be part of the first stage in ethylene glycol intoxication (Robinson and McCoy 1989; Vale 1979). In cases of acute intoxication, in which a large amount of ethylene glycol is ingested over a very short time period, there is a progression of neurological manifestations which, if not treated, may lead to convulsions and coma (Zeiss et al. 1989). Ataxia, slurred speech, and somnolence are common during the initial phase of ethylene glycol intoxication (Anonymous 1987; Parry and Wallach 1974; Zeiss et al. 1989), as are irritation, restlessness, and disorientation (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Rothman et al. 1986; Woolf et al. 1992). In a fatal case of ethylene glycol poisoning, a 22-year-old man was admitted to the hospital in a state of stupor 6 hours after ingesting 4,071 mg/kg of ethylene glycol. He vomited several times prior to admission, lost consciousness, and became comatose (Siew et al. 1975a).

Crystalline deposits of calcium oxalate in the walls of small blood vessels in the brain were found at autopsy in a man who died after acute ethylene glycol poisoning (Zeiss et al. 1989). Similar effects were observed in rats fed 2,500 mg/kg/day ethylene glycol for 13 weeks (Melnick 1984). Other neurological symptoms commonly encountered in cases of acute oral human exposure to ethylene glycol are semiconsciousness (Underwood and Bennett 1973) and unresponsiveness (Blakeley et al. 1993; Chung and Tuso 1989; Heckerling 1987; Spillane et al. 1991). More recently, several case reports described neurological symptoms associated with adverse effects of ethylene glycol on cranial nerves. These neurotoxic manifestations appear much later and according to some investigators constitute a fourth, late cerebral phase in ethylene glycol intoxication (Chung and Tuso 1989). Facial paralysis and bilateral optic nerve dysfunction were noted in a patient 13 days after ethylene glycol ingestion (Factor and Lava 1987). Delay in treatment may have contributed to the development of these symptoms; the patient was not treated until 3 days after ingesting ethylene glycol;.Severe cranial nerve dysfunction including nerves VII, IX, and X was noted in a man 5 days after he ingested 12,840 mg/kg of ethylene glycol (Spillane et al. 1991). In another case of ethylene glycol poisoning, bilateral facial paralysis and peripheral neurosensory hearing loss were observed in a patient 18 days after ingestion of 2,714 mg/kg of ethylene glycol; this effect was only partially reversible (Mallya et al. 1986).

Female Fischer 344 rats exhibited ataxia and coma prior to death after receiving 4,000 mg/kg ethylene glycol orally (Clark et al. 1979). Ethylene glycol neurotoxicity was also observed in cats given 4,440 mg/kg by gavage (Penumarthy and Oehme 1975). Neurological symptoms included abnormal gait, loss of reflexes, central nervous system depression (symptoms not specified), and convulsions. Similar signs of neurotoxicity were found in dogs after oral exposure to 4,880-10,743 mg/kg ethylene glycol (Beckett and Shields 1971; Dial et al 1994; Grauer et al. 1987). Calcium oxalate deposits were found in the brain blood vessels of rats after 13 weeks exposure to ethylene glycol in the feed (Melnick 1984).

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. In a case of acute propylene glycol poisoning, neurotoxic symptoms included stupor and repetitive convulsions (Lolin et al. 1988). The study does not specify the amount of propylene glycol that caused neurotoxicity. Various degrees of propylene glycol neurotoxicity were also observed in a group of 16 outpatients of a neurology clinic after acute oral exposure to 887 mg/kg 3 times per day for at least 3 days, using a formulation containing phenytoin and ethanol (Yu et al. 1985). Very severe mental symptoms (not specified) were observed in one patient who had the highest overall propylene glycol plasma concentration, although patients with lower plasma propylene glycol levels showed similar neurotoxicity. The estimated half-life of propylene glycol is 3.8 hours. This means that there is a measurable accumulation of propylene glycol if it is ingested in the course of a multiple-dosing regimen (Yu et al. 1985). The limitation of the study is that it does not specify if the observed propylene glycol effects may have been associated with the neurological problems already present in those patients or with concomitant ingestion of ethanol.

In a study of oral LD_{50} values using propylene glycol, lethargy and coma were observed prior to death in rats (Clark et al. 1979). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for 5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Pre-dosing observations were made such that each group of cats served as its own control. Animals were observed for signs of toxicity. Cats receiving the low dose showed no clinical signs of toxicity. Cats receiving the high dose developed decreased activity, mental depression [author's words], and slight to moderate ataxia. These cats had

high levels (44-fold higher than control) of D-lactate, thought to contribute to central nervous system toxicity. On the basis of this information, adverse neurological reactions due to exposure to low levels of propylene glycol possibly present at hazardous waste sites are very unlikely.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3, and plotted in Figure 2-3. The LOAEL value for neurological effects in rats for acute-duration category oral exposure propylene glycol is reported in Table 2-4 and plotted in Figure 2-4.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to ethylene glycol.

Results from an oral study done in mice are inconclusive. Histopathology done on testes from mice treated with 200, 400, and 1,000 mg/kg of ethylene glycol revealed marked loss of spermatogenic epithelium in a portion of the seminiferous tubules (Hong et al. 1988). The study does not indicate if one or all three doses of ethylene glycol induced this adverse effect. This effect was restricted to spermatogenic cells and did not involve Sertoli or interstitial cells. However, mice receiving 4,000 mg/kg/day ethylene glycol orally for 5 weeks did not show any pathological changes in the testis (Nagano et al. 1984). In a single mating reproductive trial, female CD-l mice were orally exposed to 250-2,500 mg/kg/day ethylene glycol for 20 consecutive days (Harris et al. 1992). On the eighth day of exposure, the females were cohabited with males that had been treated for 17 days. Females exposed to 2,500 mg/kg/day ethylene glycol had few live fetuses, more dead implants, and more litters totally resorbed. Male mice showed no treatment-related effects on the reproductive system (Harris et al. 1992). In a continuous breeding study done in CD-l mice (Lamb et al. 1985), intermediate exposure to 1% ethylene glycol in drinking water slightly decreased the fertility of the exposed parental and F_1 generations.

Dietary exposure of pregnant Fischer 344 rats to ethylene glycol (40-1,000 mg/kg/day) did not affect total implantation, or litter size (Maronpot et al. 1983). Price et al. (1985) treated rats and mice orally with doses of 1,250-5,000 mg/kg/day and 750-3,000 mg/kg/day, respectively, of ethylene glycol.

Increased postimplantation loss was observed in rats at 5,000 mg/kg/day, and in mice at 750 mg/kg/day (Price et al. 1985).

Oral administration of 50-1,500 mg/kg/day ethylene glycol to pregnant CD-l mice on Gd 6-15 had no effect on postimplantation viability (Tyl 1989). Pregnant mice given 11,090 mg/kg/day ethylene glycol on Gd 7-14 and allowed to deliver their litters exhibited a decrease in the number of viable litters, live pups per litter, and pup survival to post-parturition day (ppd) 2.5 (Schuler et al. 1984). Oral administration of 150-2,500 mg/kg/day ethylene glycol to pregnant Sprague-Dawley rats on Gd 6-15 caused no adverse effect on postimplantation viability (Neeper-Bradley 1990). However, in another study, timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Litters (38-49 per group) were fostered to untreated dams on ppd 1 and evaluated for growth, viability, developmental landmarks, locomotor activity, and learning. Live litter size and postnatal viability through ppd 4 were decreased at 2,250 mg/kg/day. Tyl et al. (1993) administered 100-2,000 mg/kg/day ethylene glycol by gavage to pregnant New Zealand White rabbits on Gd 6-19, and detected no effect on implant viability.

Fischer 344 rats were fed 40, 200, or 1,000 mg/kg/day ethylene glycol via the feed for 3 generations (DePass et al. 1986b). No changes in reproductive indices, including fertility, prenatal survival, litter size, and postnatal survival were found as a result of treatment. In an accompanying 2-year study, reproductive organs of Fischer 344 rats and CD-l mice fed up to 1,000 mg/kg/day via the feed showed no abnormal histopathology (DePass et al. 1986a; Woodside 1982).

No studies were located regarding reproductive effects in humans after oral exposure to propylene glycol.

Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation ‘period. Any offspring produced during the cohabitation period were examined, sexed, weighed, and killed to allow

continuous mating of the parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning. Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and plotted in Figure 2-3. The highest NOAEL values for reproductive effects in each species and duration category for propylene glycol after oral exposure are reported in Tables 2-4 and plotted in Figure 2-4.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to ethylene glycol.

Dietary exposure of pregnant Fischer 344 rats to ethylene glycol (40-1,000 mg/kg/day) did not affect total implantation, fetal length, fetal weight, or litter size (Maronpot et al. 1983). Vertebral malformations and rib alterations were present in both treated and control animals, but ethylene glycol did not increase the incidence of these malformations. However, there were statistically significant increases in the incidences of poorly ossified and nonossified vertebral centers in fetuses of dams receiving 1,000 mg/kg/day of ethylene glycol; the authors did not consider these to be major malformations. These findings, plus a number of external malformations, were seen. in Sprague-Dawley-derived rats and Swiss CD-l mice (Price et al. 1985) treated orally with doses of 1,250-5,000 mg/kg/day and 750-3,000 mg/kg/day, respectively, of ethylene glycol. The percentage of malformed live fetuses per litter and/or the percentage of litters with malformed fetuses were significantly elevated in all groups treated with ethylene glycol (Price et al. 1985). Reduced fetal body weight was observed at 2,500 mg/kg/day in rats, whereas reduced litter size was observed at 5,000 mg/kg/day (Price et al. 1985).

Oral administration of 50-1,500 mg/kg/day ethylene glycol to pregnant CD-l mice on Gd 6-15 caused an increase in total malformations at 500 mg/kg/day, although the increase could not be associated with individual external, visceral, or skeletal malformations (Tyl 1989). Pregnant mice given

11,090 mg/kg/day ethylene glycol on Gd 7-14 and allowed to deliver their litters exhibited a decrease in the number of viable litters, live pups per litter, pup survival, pup body weight, and body weight gain to post-parturition day (ppd) 2.5 (Schuler et al. 1984). Livebom pups of pregnant CD-l mice that were orally treated with 250-2500 mg/kg/day ethylene glycol on Gd 8-14 exhibited decreased body weight at 2,500 mg/kg/day on ppd 1 and 4 (Harris et al. 1992). Ethylene glycol at 2,500 mg/kg/day administered to pregnant Sprague-Dawley rats on Gd 6-15 caused an increase in the incidence of skeletal malformations and delayed ossification, and a decrease in fetal body weight (Marr et al. 1992). Oral administration of 150-2,500 mg/kg/day ethylene glycol to pregnant Sprague-Dawley rats on Gd 6-15 showed an increase in the incidence of individual skeletal malformations, including missing ribs and missing thoracic arches at 1,000 mg/kg/day (Neeper-Bradley 1990). Timed-mated rats were dosed by gavage on Gd 6-20 with 0, 250, 1,250, or 2,250 mg/kg/day ethylene glycol (NTP 1988). Litters (38-49/group) were fostered to untreated dams on ppd 1 and evaluated for growth, viability, developmental landmarks, locomotor activity, and learning. Decreased pup weight was observed at the high dose. Live litter size, pup weight, and postnatal viability through ppd 4 were decreased at 2,250 mg/kg/day. A significant increase in axial skeletal malformations was seen in pups from the 2,250 mg/kg/day. No adverse effects were noted in wire grasp, preweaning exploratory behavior, or visual discrimination tasks. Tyl et al. (1993) administered 100-2,000 mgAsg/day ethylene glycol by gavage to pregnant New Zealand White rabbits on Gd 6-19, and detected no effect on developmental parameters.

No studies were located regarding developmental effects in humans after oral exposure to propylene glycol.

Pregnant female Swiss mice were given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 (Kavlock et al. 1987). There was no effect of treatment on their ability to produce live pups, or on the survival of those pups. The effects of propylene glycol on reproduction of Swiss (CD-l) mice were tested in a protocol which permitted continuous breeding during a specified interval (NTP 1985). Propylene glycol in drinking water at doses of 0, 1.0, 2.5, and 5.0% yielded mean exposures of 0, 1,819, 4,796, and 10,118 mg/kg/day, based on water consumption. Animals were treated during a l-week pre-cohabitation period and a 14-week monogamous cohabitation period. Any offspring produced during the cohabitation period were examined, sexed, weighed, and killed to allow continuous mating of the -parental generation. At the end of the cohabitation period, males and females were separated, and the females were allowed to deliver and raise the last litter to weaning.

Propylene glycol had no adverse effects on any measure of reproduction, including number of litters, litter size, pup weight, or sex ratio. There was no effect on the reproductive capacity of offspring from the high dose group.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category for ethylene glycol after oral exposure are reported in Table 2-3 and plotted in Figure 2-3. The highest NOAEL values for developmental effects in each species and duration category for propylene glycol after oral exposure are reported in Table 2-4 and Figure 2-4.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to ethylene glycol. In Fischer 344 rats that received oral doses of 40, 200, and 1,000 mg/kg/day for 3 generations, there were no dominant lethal mutations (DePass et al, 1986b).

No studies were located regarding genotoxic effects in humans or animals after oral exposure to propylene glycol.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to ethylene glycol.

A 2-year oral exposure study in mice and rats (40, 200, and 1,000 mg/kg/day of ethylene glycol) produced no evidence of an oncogenic effect (DePass et al. 1984, 1986a; Woodside 1982). Furthermore, a recent 2-year. dietary study in mice indicated a lack of carcinogenic effects (NTP 1992).

Because of information available, it is reasonable to conclude that oral exposures to ethylene glycol incurred from waste site sources pose negligible risks of cancer.

No studies were located regarding cancer effects in humans after oral exposure to propylene glycol.

In a dietary study of chronic oral exposure of rats to 2,500 mg/kg/day, there were no treatment-related increases in neoplasms (Gaunt et al. 1972). Based on this information, its long history of use in consumer products, and structural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.2.3 Dermal Exposure

Dermal exposure, through activities such as changing antifreeze, is the most likely route of exposure to ethylene glycol, but dermal exposure is not likely to lead to toxic effects.

Dermal exposure to propylene glycol most likely occurs through contact with cosmetics or drugs.

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to ethylene glycol or propylene glycol. Therefore, no LOAELs for death following dermal exposure could be established. Based on the absence of data in the literature, it is unlikely that sufficient amounts of ethylene glycol or propylene glycol would be present or inhaled near hazardous waste sites to cause death among people living in the area.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal; endocrine, ocular, or metabolic effects in animals after dermal exposure to ethylene glycol.

No studies were located regarding gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans, or respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, or metabolic effects in animals after dermal exposure to propylene glycol.

The highest NOAEL values for systemic effects in each species and duration category for ethylene glycol after dermal exposure are reported in Table 2-5. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for propylene glycol after dermal exposure are reported in Table 2-6.

Respiratory Effects. Acute respiratory acidosis and cardiorespiratory arrest occurred in an 8-month-old infant with second- and third-degree burns after acute dermal treatment with silver sulfadiazine containing a high amount of propylene glycol. The dose of propylene glycol was 9,000 mg/kg/day (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects ,of both the bum injury and the sulfadiazine therapy, the actual source of the respiratory effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent.

Cardiovascular Effects. Very limited and conflicting information is available for humans on cardiovascular effects after dermal exposure to propylene glycol. An &month-old infant suffered cardiorespiratory arrest after four dermal exposures to propylene glycol in a silver sulfadiazine medication (Fligner et al. 1985). Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the cardiorespiratory effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. Other studies of propylene glycol in humans did not evaluate cardiovascular effects.

It appears that acute exposure to very high levels of propylene glycol may cause adverse cardiovascular effects, but it is unlikely that such exposures could occur as a result of being in the vicinity of hazardous waste sites.

Hepatic Effects. Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no hepatic effects (Tyl 1988b).

Renal Effects. Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no renal effects (Tyl 1988b).

TABLE 2-5. Levels of Significant Exposure to Ethylene Glycol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Systemic						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d	Hepatic	3549 mg/kg F			Tyl 1988b
		Renal	3549 mg/kg F			
		Dermal	3549 mg/kg F			
		Bd Wt	3549 F			
Rabbit (New Zealand)	once	Dermal	0.11 gm F			Clark et al. 1979
Reproductive						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d		3549 mg/kg			Tyl 1988b
Developmental						
Mouse (CD-1)	10 d Gd 6-15 6 hr/d		3549 mg/kg			Tyl 1988b

Bd Wt = body weight; d = day(s); F = female; Gd = gestational day; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level

TABLE 2-6. Levels of Significant Exposure to Propylene Glycol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
ACUTE EXPOSURE						
Systemic						
Human	5 d 1x/d	Hemato	6100 mg/kg			Commens 1990
Human	70 hr >1x/d	Resp			9000 M mg/kg (acute respiratory acidosis)	Fligner et al. 1985
		Cardio			9000 M mg/kg (cardiorespiratory arrest)	
		Metab			9000 M mg/kg (increased osmolal gap)	
Human	20-24 h	Dermal		3.2% (irritation reaction)		Hannuksela et al. 1975
Human	48 hr once	Dermal		10 mg (50% solution, skin edema and erythema)		Kinnunen and Hannuksela 1989
Human	48 hr once	Dermal		0.2 mg (1% solution, erythema and edema)		Kinnunen and Hannuksela 1989
Human	7 d 2x/d	Dermal	104 M mg			Trancik and Maibach 1982
Human	once 48 hrs	Dermal		2.5% (erythema, induration, vesiculation)		Warshaw and Herrmann 1952
Human	48 hr once	Dermal	15 mg M	31 mg M (faint, patchy erythema with edema)		Willis et al. 1988
Human	48 hr once	Dermal		16 mg M ("basket weave" pattern to stratum corneum)		Willis et al. 1989

TABLE 2-6. Levels of Significant Exposure to Propylene Glycol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rabbit (New Zealand)	once	Dermal	0.52 F gm			Clark et al. 1979
Rabbit (New Zealand)	once	Dermal	0.1 gm F			Clark et al. 1979
Immunological/Lymphoreticular						
Human	20-24 hr			3.2% (allergic reaction)		Hannuksela et al. 1975
Neurological						
Human	70 hr >1x/d				9000 M mg/kg (hypoxic encephalopathy)	Fligner et al. 1985
INTERMEDIATE EXPOSURE						
Systemic						
Human	21-22 d	Dermal		207 mg M (erythema)		Trancik and Maibach 1982

Cardio = cardiovascular; d = day(s); F = female; Hemato = hematological; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; NOAEL = no-observable-adverse-effect level; Resp = respiratory; x = times

2. HEALTH EFFECTS

Dermal Effects. Skin irritation was minimal in New Zealand White rabbits 24-72 hours after application of 0.55 grams ethylene glycol to shaved skin (Clark et al. 1979). Pregnant female mice exposed to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application showed no dermal effects (Tyl 1988b).

Propylene glycol does not seem to have significant irritative properties. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm2 of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of-the findings from these studies, the authors concluded that propylene glycol has marginal irritant properties. However, some cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients, applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water, caused approximately 208 patients to show some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of cornea1 cells producing a characteristic "basket weave" pattern in the stratum comeum (Willis et al. 1989). In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forstrijm 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 36-48 hours without any medications.

During 1951 and 1952, propylene glycol was applied in a covered patch test to the normal skin of 866 patients (Warshaw and Herrmann 1952). The test sites were examined 48 hours after application of the patches. Undiluted propylene glycol (Brand A, B, and C), and aqueous dilutions-of Brand A (2.5, 10, and 50%) were tested. Related compounds, including glycerine, and carbowax 1,500, were also tested. Propylene glycol was also applied directly to the skin of some individuals with a glass rod for 20 seconds. The application site was left uncovered. In many of the patients, the patch tests were repeated, but in different locations. When possible, the patients were re-tested after a period of several months. Several patients who reacted to propylene glycol were re-tested with exposure to propylene

glycol and dry heat; female patients who reacted to propylene glycol received lipsticks containing propylene glycol for trial use. Positive results were observed in 138 (15.7%) of the skin patch tests of propylene glycol. The reactions ranged from simple erythema to erythema with induration and vesiculation. No differences were noted in reactions to different brands of propylene glycol. Twenty-three persons with reactions to pure propylene glycol were tested with 50 and 10% dilutions. In general, the reaction to propylene glycol decreased with decreasing concentration. Only 5 of 23 showed any reaction to 10% propylene glycol, and only showed simple erythema. One of three persons tested with 2.5% propylene glycol had a positive reaction. Sixteen patients with positive reactions to the propylene glycol patch test were further patch-tested with glycerine and carbowax 1500, yielding 1 positive reaction to carbowax 1500, and a questionable positive reaction to glycerine. Sixteen patients with positive reactions to the patch test with propylene glycol were retested by simple application of propylene glycol. No positive reactions were observed. The incidence of positive reactions to propylene glycol appeared to fluctuate with the season, and was significantly higher during the cooler and less humid months (14-22% from October to June, 6% from July to September). In 23 of the positive reacting patients, the patch tests with propylene glycol were repeated after a period of 2-12 months. Seventeen of 23 patients showed a positive response, while the other 6 showed no response. Repeated testing with increased heat and moisture, reactivity tended to decrease. One of 15 female patients with a positive reaction to the propylene glycol patch test was also reactive to lipstick containing propylene glycol which was applied to the lips.

Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered' allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol. applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5% showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 showed a positive reaction to 10%,

and 9 of 42 had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a lo-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 21-day cumulative irritation test was conducted using propylene glycol (Trancik and Maibach 1982). Ten Caucasian males with healthy skin received dermal applications of 207 mg propylene glycol (USP) on their backs in the same spot every day for 21 days. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reaction to intense erythema with edema and vesicular erosion. In the 21-day cumulative irritation test, only one subject presented with a reaction, which was rated as equivocal irritation, on 20 of the test. All other subjects in the test had no reaction. Results of the 21-day cumulative irritation test indicates that propylene glycol is at least a minimal irritant.

There are few studies of dermal effects of propylene glycol in animals. New Zealand White rabbits exposed to 0.52 g of propylene glycol on skin showed little or no irritation after 72 hours (Clark et al. 1979).

These findings, plus a long history of safe use in medicine, indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity or other skin reactions in the human population living in the vicinity.

Ocular Effects. Little or no eye irritation was noted after instillation of 0.11 g ethylene glycol in the eye of rabbits (Clark et al. 1979).

Body Weight Effects. Pregnant CD-l mice showed no changes in body weight after exposure to 3,549 mg/kg/day ethylene glycol for 6 hours per day on Gd 6-15 by occluded dermal application (Tyl 1988b).

Metabolic Effects. High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. Increased osmolal gap was found in two cases of acute dermal exposure to propylene glycol. An S-month-old infant with a severe bum was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). The osmolal gap reached a maximum of 130 rnilliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. The bum injury may have contributed to the increased absorption of propylene glycol and hence, the hyperosmolality. However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding immunological and lymphoreticular effects in animals after dermal exposure to propylene glycol.

Since propylene glycol is widely used as a vehicle for dermally applied medications, several studies investigated its potential as both an irritant and contact allergen. Skin testing of 42 healthy volunteers showed that 100% propylene glycol caused faint, patchy erythema with edema in 40% of the tested subjects (Willis et al. 1988). In another study, an acute dermal exposure of eczema patients to 0.2 and 22.8 mg/cm’ of propylene glycol caused skin edema and erythema in 3.8% of the 823 patients that were skin tested (Kinnunen and Hannuksela 1989). On the basis of the findings from these two studies, the authors concluded that propylene glycol has marginal irritant properties. However, some

cases of sensitivity have been recorded in the literature. A 51-year-old woman developed a severe itchy erythematous vesicular dermatitis of the upper lip, nose, and adjoining right cheek after applying a cream containing 10% propylene glycol (Corrazza et al. 1993). A patch test revealed a sensitivity to propylene glycol. In a test of 1,226 patients applying 5% propylene glycol in Vaseline, or 10, 30, or 50% in water resulted in approximately 208 patients showing some reaction (Aberer et al. 1993). Of these 208 patients, 195 exhibited some form of irritation, whereas only 13 exhibited an allergic reaction (Aberer et al. 1993). The mechanism of the reaction is not understood, but electron microscopy revealed that propylene glycol causes hydration of comeal cells producing a characteristic "basket weave" pattern in the stratum comeum (Willis et al. 1989): In order to determine if propylene glycol can also evoke a hypersensitivity reaction, a total of 15 patients who had positive skin reactions to propylene glycol were exposed to an acute oral propylene glycol challenge (Hannuksela and Forström 1978). The hypersensitivity reaction that developed consisted of exanthem and cleared within 36-48 hours without any medications. Propylene glycol was tested on the skin of 1,556 patients with eczema using a chamber on the back of the patients (Hannuksela et al. 1975). Undiluted propylene glycol was applied to the backs of the patients and left there for 20-24 hours. Readings of the exposure area were made 1, 2, and 4-5 days after application of the chemical. Reactions with redness, with or without infiltration peaking on the first day were considered irritant reactions. Reactions with infiltration with or without vesiculation extending to a considerably larger area than the test area, with the maximum occurring on the second day or later were considered allergic. Forty-two positive reactors were subjected to patch tests with 3.2, 10, or 32% aqueous propylene glycol. Fifteen patients with allergic reactions to propylene glycol applied undiluted propylene glycol to their armpits 3 times daily for 4 days. Of the patients tested with undiluted propylene glycol, 12.5% showed positive reactions. Of these, 70% were of primary irritation, and 30% were allergic in appearance. Seasonal variation was observed, with more cases observed in the winter. Forty-two cases of positive reactions to undiluted propylene glycol were retested with aqueous dilutions of the compound. Twelve of 42 cases showed a positive reaction to lo%, and 9 of 42 cases had a reaction to 3.2%; 20 of 42 cases reacted to the 32% solution. Eleven of 15 patients who applied propylene glycol to their armpits had no reaction. The 4 reacting patients exhibited itching 4-10 hours and eczema within 24 hours. The symptoms reached their peak at 48 hours and disappeared after 3-5 days. Three of these patients used undiluted propylene glycol and one patient used 10% propylene glycol. In this latter patient, examination of the skin of a lo-hour-old reaction revealed no change in the epidermis, but perivascular infiltration in the dermis, indicative of an allergic reaction.

A 22-day sensitization procedure was conducted using propylene glycol (Trancik and Maibach 1982). For the sensitization procedure, 203 Caucasian males with healthy skin received dermal doses of 207 mg propylene glycol on their backs on Mondays, Wednesdays, and Fridays for 22 days, resulting in a total of 10 doses. The application site was occluded for 48-72 hours (i.e., covered between doses). The test sites were read when the patches were changed. The application site was occluded with gauze and tape for 24 hours following application. Daily readings of test site were conducted at the time the patches were removed. Scoring ranged from no visible reactionto intense erythema with edema and vesicular erosion. In addition, minimal glazing of the skin (roughness) was added to the scoring list. Two weeks after the sensitization phase, a challenge dose was applied to previously untested skin and occluded for 48-72 hours. Rechallenge was performed at 2-week intervals. In the sensitization test, equivocal responses were noted, but no reaction more than equivocal was observed. At the challenge, 19 of 203 showed a positive response. Upon rechallenge, five exhibited an increase in response. The sensitization test indicates that propylene glycol might be a sensitizer.

These findings plus a long history of safe use in medicine indicate that prolonged dermal exposure to the low levels of propylene glycol present at hazardous waste sites is very unlikely to cause hypersensitivity reactions in the human population living in the vicinity.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding neurological effects in animals after dermal exposure to propylene glycol.

Adverse neurological reactions were observed in patients who tested positive in a propylene glycol patch test after an acute oral challenge with 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). Although the observed neurotoxicity is attributed to propylene glycol, the study reports that this response was seen in allergic individuals. An 8-month-old infant with a severe bum was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). After developing respiratory acidosis, the infant experienced cardiac arrest and was resuscitated. Subsequent neurological examination revealed hypoxic damage, which was evident by

persistent hypoxic encephalopathy. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the respiratory effect and subsequent neurological damage in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent.

The LOAEL value for neurological effects in humans for acute effects for propylene glycol after dermal exposure is reported in Table 2-6.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to ethylene glycol.

Pregnant CD-l mice exposed to ethylene glycol at doses up to 3,549 mg/kg on Gd 6-15 by occluded dermal application exhibited no adverse reproductive effects (Tyl 1988b).

No studies were located regarding reproductive effects in humans or animals after dermal exposure to propylene glycol.

The highest NOAEL value for reproductive effects in mice for the acute-duration category for ethylene glycol after dermal exposure are reported in Table 2-5

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to ethylene glycol.

Pregnant CD-l mice exposed to ethylene glycol at doses up to 3,549 mg/kg on Gd 6-15 .by occluded dermal application exhibited no adverse developmental effects, including fetal weight and morphological development (Tyl 1988b).

No studies were located regarding developmental effects in humans or animals after dermal exposure to propylene glycol.

The highest NOAEL value for developmental effects in mice for the acute-duration category for ethylene glycol after dermal exposure is reported in Table 2-5.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to ethylene glycol or propylene glycol.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to ethylene glycol.

No studies were located regarding cancer effects in humans after dermal exposure to propylene glycol.

No increase in tumors was observed after twice weekly applications of propylene glycol to the skin of Swiss mice for 120 weeks, at doses up to 2 mg (Stenback and Shubik 1974). Based on this information, its long history of use in consumer products, and stmctural activity considerations, it is extremely unlikely that exposure to levels of propylene glycol near hazardous waste sites would influence the incidence of cancer in the population living in the vicinity.

2.3 TOXICOKINETICS

The toxicokinetics of ethylene glycol is fairly well understood. Data from inhalation studies are relatively scarce; dermal studies are somewhat more numerous. Most of the kinetic data for ethylene glycol comes from oral exposures. Absorption, distribution, metabolism, and excretion have been monitored for ethylene glycol. Production of toxic metabolites is critical to the toxicity of ethylene glycol. These aspects are discussed below.

The toxicokinetics of propylene glycol is less well defined. Dermal data are most abundant for propylene glycol. Due to the relatively nontoxic nature of the compound, kinetic data are somewhat scarce. Available information is discussed below.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No kinetic data for absorption in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.1.2 Oral Exposure

Since human exposure to ethylene glycol is usually oral by accidental means, or intentional ingestion without records of the amount ingested, data describing absorption of ethylene glycol after human oral exposure were not found in the literature.

In rats, ingested ethylene glycol is rapidly absorbed and evenly distributed throughout the body reaching peak blood levels l-4 hours after ingestion of doses of 7-29 mg/kg (Winek et al. 1978). Recovery of ethylene glycol after oral exposure of rats and mice to doses up to 1,000 mg/kg is approximately 90-100%, indicating substantial absorption (Frantz et al. 1989, 1991). Serum levels of ethylene glycol in dogs suspected to have ethylene glycol intoxication from oral exposure were 0.148-4.080 g/dL (Dial et al. 1989). When Dial et al. (1994) conducted a controlled study of ethylene glycol toxicity in dogs after oral administration, semm blood levels of ethylene glycol were determined in animals receiving 4-methyl pyrazole, an alcohol dehydrogenase inhibitor, 5 or 8 hours after ingestion of 10,070-10,600 mg/kg ethylene glycol. Serum concentration peaked 6 hours after exposure in both treatment groups. Peak level were approximately 900 mg/dL in dogs treated 5 hours after ethylene glycol ingestion, and 800 mg/dL in dogs treated 8 hours after ethylene glycol ingestion.

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure (Yu et al. 1985). An equal number (5-6) of cats of both sexes were fed a diet containing 12% propylene glycol (low dose, 1,600 mg/kg/day) for

5 weeks, a dose equivalent to that found in commercial soft-moist cat foods, or a high dose diet containing 41% propylene glycol (8,000 mg/kg/day) for 22 days (Christopher et al. 1990b). Predosing observations were made such that each group of cats served as its own control. Plasma levels of propylene glycol were measured in 2 cats fed the low dose on day 24 of ingestion, and compared to pre-dosing samples. Plasma levels of propylene glycol were 19.1 and 8.4 mmol/liter for the 2 cats.

2.3.1.3 Dermal Exposure

Since human exposure to ethylene glycol is often dermal by accidental means, without records of the amount, data describing absorption of ethylene glycol after *in vivo* human exposure were not found in the literature. The in vitro permeability of human skin to ethylene glycol was determined by Loden (1986). The rate of resorption was 118 μg/cm^2/hour, with a steady state concentration of 0.97 mg/cm^2. Additional *in vitro* studies of dermal absorption of ethylene glycol have been conducted. The percutaneous absorption of [^{14}C]ethylene glycol through human skin was evaluated (Driver et al. 1993). Radiolabeled ethylene glycol was applied to the surface of three different fresh human skin samples at a dose of 8 μg/cm^2. After 24 hours of exposure, 18.3% of the applied dose was recovered from the receptor fluid (absorbed through the skin), 8.3% in the skin, and 12.5% in the skin surface, for a total of approximately 39% recovery of the applied dose. Individual differences existed for the three samples; average potential absorption was 26.6%. This represented an absorption rate of approximately 0.09 μg/cm^2/hour for ethylene glycol.

In dermal applications using an occlusion bandage, approximately 30% of doses of ethylene glycol up to 1,000 mg/kg was absorbed through rat skin (Frantz et al. 1989), whereas mice absorbed 85-100% of the administered dose (Frantz et al. 1991). Thus, some species differences exist in the permeability of animal skin to this chemical.

Some studies of the dermal absorption of propylene glycol have been conducted. Patients with second and third degree bums over more than 20% of their total body surface were studied over a period of 30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average serum levels were 0.08 mg/mL, with a range of 0-1.3 mg/mL for patient who lived, and 0.82 mg/mL with a range of 0-9.8 mg/mL for patients who

died. Propylene glycol levels correlated with total bum surface area and total third degree bum surface area.

In vitro studies of the penetration of propylene glycol through rat abdominal stratum comeum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis.

Comparison of propylene glycol absorption by skin from humans, hairless mice, and snakes was conducted (Rigg and Barry 1990). Shed snake skin tended to underestimate propylene glycol absorption in human skin, especially in the presence of enhancers, whereas hairless mouse skiu greatly overestimated absorption compared to human skin. The authors concluded that human skin should be used for absorption studies whenever possible.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No kinetic data for distribution in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.2.2 Oral Exposure

The apparent volume of distribution of ethylene glycol has been determined by calculation from clearance data in two patients, to be 0.54 and 0.56 L/kg (Jacobsen et al. 1988). Also, the urine to

plasma concentration ratios for several ethylene glycol determinations in one patient were about 1.0-1.4, similar to those of ethanol. These data suggest a total body water distribution for ethylene glycol.

In rats, 10-20% of oral doses up to 1,000 mg/kg of ethylene glycol were recovered from the body tissues and carcass 96 hours after a single dose (Frantz et al. 1989), whereas mice retained only a small percentage of the dose in their tissues (Frantz et al. 1991).

No studies of the distribution of propylene glycol in humans or animals after oral exposure were found in the literature.

2.3.2.3 Dermal Exposure

Distribution of a 100 or 1,000 mg/kg cutaneous undiluted dose of radiolabled ethylene glycol or a 1,000 mg/kg dose of a 50% aqueous solution of ethylene glycol using an occlusive bandage was determined in mice (Frantz et al. 1991). At 100 mg/kg undiluted ethylene glycol, 99.5% of the dose was recovered, with tissues and excreta accounting for 76.5%. Most was recovered as volatile organic radioactivity (2-S39%) or as radioactive CO_2 (8-12%). Urine and feces each accounted for another 4-9% of the dose. Tissue recoveries were less than 1% of the dose, while the residual carcass contained about 10-18% of the dose. Cage wash water and the bandage itself accounted for the rest of the dose. Following the 1,000 mg/kg undiluted ethylene glycol application, total recovery was 89% of the dose: 84% in tissues and excreta, and approximately 7% in feces, cage wash water, and carcass. Recovery from the 1,000 mg/kg dose in 50% aqueous solution was similar to the undiluted dose. Tissue recoveries for all three doses were similar, with the liver showing the highest level (0.58-0.59%), followed by the kidney (0.06-0.07%), the brain and lung (0.02-0.03% each), the REKs (0.009-0.014), plasma (0.008-0.009%), and fat (0.005-0.008%).

In vitro studies of the penetration of propylene glycol through rat abdominal stratum corneum have been conducted (Takeuchi et al. 1993, 1995). Fresh abdominal skin from male Wistar rats was used in experiments in which propylene glycol, or a mixture of propylene glycol and oleic acid were evaluated for absorption properties (Takeuchi et al. 1993). When propylene glycol was applied alone for up to 2 hours, no compound was detected in the dermis. However, when 0.15 M oleic acid was added to the propylene glycol, propylene glycol was detected in the dermis after 30 minutes of exposure, but

not after 5 or 15 minutes (Takeuchi et al. 1993). The appearance of propylene glycol seemed to be in three phases when in the presence of a skin penetration enhancer such as oleic acid (Takeuchi et al. 1995). The first stage was the penetration of propylene glycol into the skin barrier, without any change of the dermal structure. The second stage was rapid distribution in and throughout the dermis, presumably accompanied by alteration of the dermal structure. In the third stage, propylene glycol was saturated in the dermis. Additional evaluation indicated that the volume of distribution of propylene glycol in the dermis was influenced by the efficiency of the enhancer compound, with oleic acid and oleylamine being the most efficient, compared to lauric acid, laurylamine, or azone.

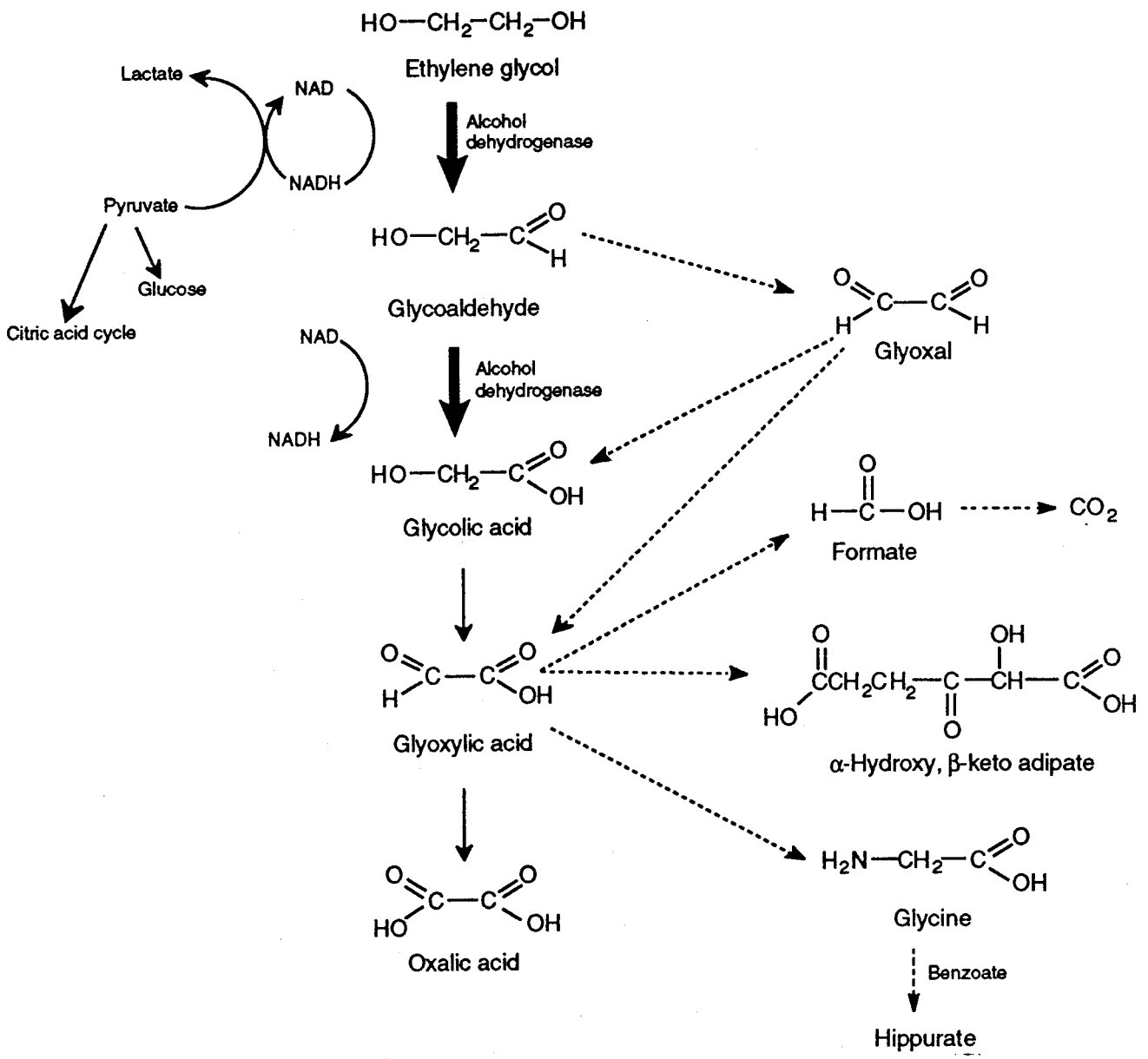
2.3.3 Metabolism

The metabolic pathway for ethylene glycol is shown in Figure 2-5. Solid arrows in Figure 2-5 represent the steps that are quantitatively most important while the broken arrows indicate minor metabolic conversions in humans. Knowledge of ethylene glycol metabolism helps one understand its mechanism of action, the pathogenesis of its toxicity, and the rationale for treatment of acute ethylene glycol intoxication. This knowledge comes from studies investigating oxidative biodegradation of ethylene glycol. Ethylene glycol is oxidized to glycolaldehyde by nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase in the liver and kidney. Glycolaldehyde is further oxidized to glycolic acid by mitochondrial aldehyde dehydrogenase and cytosolic aldehyde oxidase; glycolic acid is oxidized to glyoxylic acid by glycolic acid oxidase or lactic dehydrogenase. The enzyme catalyzing the formation of oxalic acid from glyoxylic acid is glycolic acid oxidase. Glyoxylate can induce lactic acid formation via oxalomalate production and its inhibitory effects on the citric acid cycle (Gabow et al. 1986; Jacobsen et al. 1988; Parry and Wallach 1974; Robinson and McCoy 1989; Vale 1979; Wiener and Richardson 1988).

The levels of plasma glycolate were determined in 3 cases (2 female infants and 1 adult male) of accidental ethylene glycol intoxication (Hewlett et al. 1986). Plasma levels of glycolate ranged from 12.2-15.4 mmol/L. The infants survived, and the adult male died, probably due to delayed treatment for metabolic acidosis. In another study with 6 patients, one of whom died, plasma glycolate levels on admission ranged from 17.0-29.3 mmol/L (Jacobsen et al. 1984)

In rats given 200 mg/kg ethylene glycol by gavage, peak plasma levels of ethylene glycol occurred 2 hours after administration, while plasma glycolate levels peaked 4 hours after dosing (Hewlett et al.

Figure 2-5. Metabolic Pathway for Oxidation of Ethylene Glycol



Adapted from Gabow et al. 1986; Jacobsen et al. 1988; Robinson and McCoy 1989; Vale 1979; Wiener and Richardson 1988.

1989). Dogs receiving 100 or 136 mg/kg ethylene glycol by gavage exhibited peak ethylene glycol levels at 2 hours after dosing (Hewlett et al. 1989). Male Porton rats receiving 999-1,110 mg/kg ethylene glycol in the drinking water for 21 days exhibited urinary oxalate levels equivalent to 1.18% conversion of ethylene glycol to oxalate; rats given diets supplemented with 30% or 60% sucrose excreted oxalate equivalent to 1.11 and 0.7% conversion of ethylene glycol, respectively (Rofe et al. 1986).

The metabolic pathway for propylene glycol in mammals is shown in Figure 2-6. Commercially available propylene glycol is usually a mixture of D- and L-isomers. The major route of metabolism for propylene glycol is via alcohol dehydrogenase to lactaldehyde, then to lactate, via aldehyde dehydrogenase, and on to glucose through gluconeogenic pathways (as summarized in Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1989, 1991b; Ruddick 1972). Conversion to methylglyoxal is an alternate route via alcohol dehydrogenase, ending in metabolism to D-lactate through glyoxalase.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

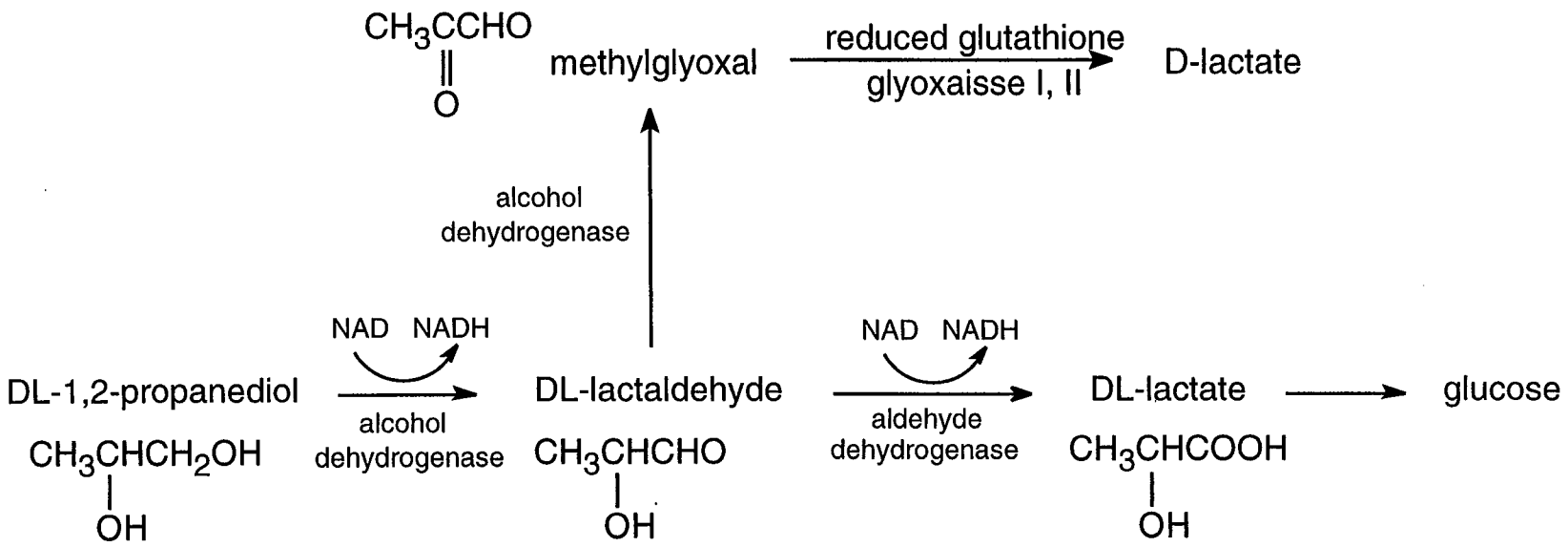
No kinetic data for excretion in humans or animals of ethylene glycol or propylene glycol after inhalation exposure were found in the literature.

2.3.4.2 Oral Exposure

Approximately 24-48 hours after ethylene glycol ingestion, it is difficult to detect ethylene glycol in either urine or tissues (Winek et al. 1978); this supports its relatively rapid biotransformation. The approximate serum half-life of ethylene glycol is 2.5 hours for children (Rothman et al. 1986), and 2.7 hours for adults during hemodialysis (Cheng et al. 1987). In untreated adults, the serum half-life has been estimated to be between 3.0 and 8.4 hours (Jacobsen et al. 1988; Peterson et al. 1981).

The elimination half-life for ethylene glycol in the plasma has been estimated at 1.7 and 3.5 hours in rats and dogs given 2,000 mg/kg and l,000-1,360 mg/kg, respectively; 1.4-2.5 hours in rats given 10-1,000 mg/kg; and 0.3-1.1 hours in CD-l mice given 10-1,000 mg/kg (Frantz et al. 1989, 1991;

Figure 2-6. Propylene Glycol Metabolism in Mammals



From Christopher et al. 1980b

Hewlett et al. 1989). All kinetic parameters were determined in the terminal phase of elimination after oral dosing. Data from intravenous administration of ethylene glycol show similar elimination halflives (Frank et al. 1989, 1991; Martis et al. 1982).

In rats given oral doses of radioactive ethylene glycol up to 1,000 mgkg, the major excretory route of ^{14}C was via CO_2 exhalation (42%), while 24% of the dose was excreted via the urine and 3% via the feces (Frantz et al. 1989). Mice showed a similar profile, exhaling 55% of the dose, and excreting 24% in the urine and up to 12% in the feces (Frantz et al. 1991). The majority of the exhaled radioactivity was eliminated during the first 12 hours after dosing (Frantz et al. 1989, 1991). In contrast, approximately 50% of an oral dose of ethylene glycol administered to dogs was excreted via the urine (Grauer et al. 1987).

When Dial et al. (1994) conducted a controlled study of ethylene glycol toxicity in dogs after oral administration, serum half-life of ethylene glycol was determined in animals receiving 4-methyl pyrazole, an alcohol dehydrogenase inhibitor, 5 or 8 hours after ingestion of 10,070-10,600 mg/kg ethylene glycol. The half-life was 7 hours in dogs treated 5 hours after ethylene glycol ingestion, and 15 hours in dogs treated 8 hours after ethylene glycol ingestion. Urine concentration peaked 3 hours after ethylene glycol ingestion in dogs treated after 5 hours, and at 9 hours in dogs treated 8 hours after exposure. The percentage of ethylene glycol excreted unchanged was significantly greater in dogs treated 5 hours after ingestion, compared to dogs treated 8 hours after ingestion.

The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about, 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serum-concentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). An apparent maximum elimination rate of 8.3 mmol/kg/hour (630 mg/kg/hour) was observed.

2.3.4.3 Dermal Exposure

After dermal application of ethylene glycol, rats absorbed only 31% of doses up to 1,000 mg/kg, 14% of the absorbed dose was expired, while 7% was excreted in the urine, and 1% was recovered from the

feces (Frantz et al. 1989). Distribution of a 100 or 1,000 mg/kg cutaneous undiluted dose of radiolabled ethylene glycol or a 1,000 mg/kg dose of a 50% aqueous solution of ethylene glycol using an occlusive bandage was determined in mice (Frantz et al. 1991). At 100 mg/kg undiluted ethylene glycol, 99.5% of the dose was recovered, with tissues and excreta accounting for 76.5%. Most was recovered as volatile organic radioactivity (25-39%) or as radioactive CO_2 (8-12%). Urine and feces each accounted for another 4-9% of the dose. Tissue recoveries were less than 1% of the dose, while the residual carcass contained about 10-18% of the dose. Cage wash water and the bandage itself accounted for the rest of the dose. Following the 1,000 mgkg undiluted ethylene glycol application, total recover was 89% of the dose: 84% in tissues and excreta, and approximately 7% in feces, cage wash water, and carcass. Recovery from the 1,000 mgkg dose in 50% aqueous solution was similar to the undiluted dose.

Excretion of propylene glycol has been studied in humans. Patients with second and third degree bums over more than 20% of their total body surface were studied over a period of 30 months (Kulick et al. 1985). Sulfadiazine preparations containing propylene glycol were applied dermally over a period of 3-7 days after admission to the hospital. Serum and urinary levels of propylene glycol were measured. Propylene glycol was detected in the serum of 24 of 45 patients, and in the urine of 40 of 45 patients. Average urinary levels were 1.3 mg/rnL, with a range of 0-17.9 mg/mL for patient who lived, and 2.9 mg/mL with a range of 0-23.0 mg/mL for patients who died. Propylene glycol levels correlated with total bum surface area and total third degree bum surface area.

2.3.5 Mechanism of Action

The mechanism of action of ethylene glycol can be best explained by describing the main effects that follow its ingestion: increased osmolal gap, metabolic acidosis, and formation of calcium oxa.late crystals. The elucidation of ethylene glycol metabolism (Figure 2-5) has helped in the understanding of its mechanism of toxic action.

In the initial stages after ingestion of ethylene glycol, its concentration in extracellular fluids increases, leading to increased osmolality. This increased osmolality (hyperosmolarity) further leads to an increased osmolal gap, one of the hallmarks of ethylene glycol intoxication. Osmolal gap is defined as a difference between the measured and calculated osmolality. Osmolality (calculated) can be estimated from the formula that takes into account normal serum concentrations of sodium, glucose, and BUN.

This calculated osmolality is then compared to the serum osmolality measured following ethylene glycol ingestion; a difference greater than 10 indicates an increased osmolal gap (Fligner et al. 1985). The increased osmolal gap is not solely characteristic of ethylene glycol intoxication and can occur when any osmotically active, non-measured solute (e.g., mannitol) is present in the serum. In dogs given oral doses of 10,743 mg/kg ethylene glycol, serum osmolality peaked (460 milliosmoles/kg) at 3-6 hours, and the osmolal gap peaked (134 milliosmoles/kg) at 3 hours, coinciding with peak serum ethylene glycol levels at 3 hours (Grauer et al. 1984). In these animals, the anion gap was also significantly increased at 3 hours (19 Meq/L).

The second characteristic of ethylene glycol intoxication is metabolic acidosis. Ethylene glycol itself has low toxicity (Godolphin et al. 1980; Jacobsen and McMartin 1986), but it is metabolized to a variety of toxic metabolites such as glycolaldehyde, glycolic acid (glycolate), glyoxylic acid (glyoxylate), and oxalic acid (oxalate) (Jacobsen et al. 1988; Parry and Wallach 1974; Vale 1979; Wiener and Richardson 1988). In general, the accumulation of acids leads to acidosis, a state that is characterized by actual or relative decrease of alkali in body fluids in relation to the acid content. In the case of ethylene glycol, metabolic processes that follow ethylene glycol ingestion lead to the accumulation of glycolic and lactic acids resulting in metabolic acidosis. The assumption that ethylene glycol toxicity is due to its metabolic products is made because there is a latent period before the symptoms of acidosis appear, because there is no correlation between observed toxicity and ethylene glycol blood concentration, and because inhibition of ethylene glycol oxidation prevents toxicity (Jacobsen and McMartin 1986). Furthermore, glycolic acid is the most abundant of all ethylene glycol metabolites (Jacobsen et al. 1984). Following ingestion of high doses of ethylene glycol, glycolic acid tends to accumulate because it is a substrate for lactic dehydrogenase and/or glycolic acid oxidase.

The accumulation of metabolites such as glycolic acid, oxalate, and lactic acid leads to an increased anion gap and metabolic acidosis, which are responsible for toxicity observed after ethylene glycol ingestion. While lactate levels increase in some human cases up to 5-7 mmol (Jacobsen et al. 1984, 1988; Parry and Wallach 1974), glycolate levels range up to 20-25 mmol, thus accountiiig for a greater portion of the anion gap. The serum anion gap is calculated by subtracting the sum of the serum chloride and bicarbonate ions from serum sodium ions. In dogs given oral doses of 10,743 mg/kg ethylene glycol, the anion gap was significantly increased at 3 hours (19 Meq/L) coinciding with peak serum ethylene glycol levels (Grauer et al. 1984). The maximum production of metabolites occurs 6-12 hours after ethylene glycol ingestion and coincides with neurotoxicity.

Ethylene glycol metabolites inhibit oxidative phosphorylation, respiration, glucose metabolism, protein synthesis, deoxyribonucleic acid (DNA) replication, ribosomal ribonucleic acid (RNA) synthesis, central nervous system respiration, and serotonin metabolism (Vale 1979). Glycolic acid and lactic acid are the major and minor contributors, respectively, to the production of metabolic acidosis, one of the hallmarks of acute ethylene glycol intoxication.

Nephrotoxicity and neurotoxicity can follow because oxalate can produce renal and brain damage as it chelates with calcium ions forming insoluble calcium oxalate. monohydrate crystals, another characteristic of ethylene glycol poisoning (Jacobsen et al. 1988). This may lead to hypocalcemia and imbalance of serum divalent ion concentrations (Zeiss et al. 1989). Although the mechanism of ethylene glycol neurotoxicity is not completely understood, the available information on humans suggests that it occurs in two stages, an early one (30 minutes to 12 hours after exposure) and a late one (several days after exposure). The early-stage symptoms are due to the direct toxicity of ethylene glycol, while the late-stage neurotoxicity is due to metabolic acidosis caused by the accumulation of ethylene glycol metabolites, primarily glycolic acid, which leads to metabolic acidosis. Additional evidence for this late neurotoxicity is crystalline deposits of calcium oxalate in the walls of small blood vessels found in the brain of a man who died of acute ethylene glycol poisoning (Zeiss et al. 1989). Similar effects were observed in rats fed 2,500 mg/kg/day ethylene' glycol for 13 weeks (Melnick 1984). The role of calcium in ethylene-glycol-induced neurotoxicity is not known but the formation of calcium oxalate crystals may cause perturbation of intracellular calcium homeostasis causing membrane abnormalities generally associated with cell injury and cell death.

The presented data indicate that glycolic acid is the major toxic metabolite contributing to metabolic acidosis, which is a primary cause of systemic toxicity following exposure to ethylene glycol.

The mechanism of action of propylene glycol is not well understood.

2.4 RELEVANCE TO PUBLIC HEALTH

Ethylene glycol is a chemical that is common in many consumer products, including antifreeze, de-icing solutions, printer's ink, stamp pads, and ballpoint pen ink. It is widely sold in grocery, hardware, and home supply stores. In addition, it is used for de-icing airplanes and other machinery; generation of artificial smokes, mists, and fogs; and in the manufacture of polyester fibers, and various

paints and coatings. By far, the most common route of exposure to ethylene glycol is dermal, through the process of changing the antifreeze in an automobile. However, most of the human toxicity data has been derived from accidental or intentional ingestion of ethylene glycol. There are often three stages of oral ethylene glycol toxicity in humans. They are well documented and occur within 72 hours after ingestion (Robinson and McCoy 1989; Vale 1979). The first stage involves central nervous system depression, metabolic changes (hyperosmolality and acidosis), and gastrointestinal upset, and spans the period from 30 minutes to 12 hours. During the second stage of ethylene glycol toxicity (12-24 hours after ingestion), cardiopulmonary symptoms (tachypnea, hyperpnea, and tachycardia) become evident. These symptoms are largely due to metabolic acidosis. During stage three, which covers the period 24-72 hours after ethylene glycol ingestion, renal involvement becomes evident. The third stage is characterized by flank pain and oliguria/anuria. The histopathological findings show renal tubular necrosis and deposition of calcium oxalate crystals (Vale 1979). Often the cardiopulmonary effects in the second stage are not evident, so the distinguishing symptoms of ethylene glycol intoxication are central nervous system depression, acidosis, and nephrotoxicity (Jacobsen and McMartin 1986; Karlson-Stilber and Persson 1992). One study defines a fourth stage as the late cerebral stage that occurs 6-13 days after ethylene glycol ingestion (Chung and Tuso 1989). Animal studies include exposure by inhalation, oral and dermal routes. Many of the same toxic events that have been identified in humans after oral exposure have been identified in animals as well.

Propylene glycol is a colorless, odorless, water-soluble liquid considered safe for use in commercial formulations of foods, drugs, and cosmetics. Propylene glycol, like ethylene glycol, is used as an antifreeze, de-icing solution, and in various paints and coatings. Unlike ethylene glycol, however, propylene glycol has been approved as safe in various food flavorings, drugs, cosmetics, and as a direct additive to food. Propylene glycol is commonly used in the pharmaceutical industry as a solvent for drugs, as a stabilizer for vitamins, and in ointment for medicinal applications. Propylene glycol may be found in canned fruit, packaged coconut, as a solvent in drug and cosmetic preparations, and in flavorings and extracts. Propylene glycol is also used in the generation of artificial mists and fogs used in fire safety training, and theatrical and stage productions: This widespread use of propylene glycol stems from its low level of toxicity.

Minimal Risk Levels for Ethylene Glycol

Inhalation MRLS

- An MRL of 0.5 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ethylene glycol.

The MRL was based on a NOAEL of 197 ppm for increased renal weight (Tyl 1988a). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability) and adjusting for the intermittent exposure (6/24 hours). Timed-pregnant CD-l mice were exposed to ethylene glycol aerosol on Gd 6-15, 6 hours per day by nose-only procedures at doses of 0, 500, 1,000, or 2,500 mg/m3 (0, 197, 394, or 985 ppm) target concentration (Tyl 1988a). Control animals were exposed to water aerosol (4,200 mg/m^3 or 5,705 ppm). Females were weighed, observed daily for clinical signs, and evaluated for water consumption. At termination on Gd 18, females were evaluated for body weight, gravid uterine weight, liver weight, and kidney weight. Ovarian corpora lutea were counted and all uterine implantation sites evaluated. Maternal body weight was unaffected. No dose-related clinical signs were noted. Water consumption was not significantly affected. At termination, liver weight was not affected. Absolute maternal kidney weight was increased at 394 and 985 ppm and relative maternal kidney weight was increased at 985 ppm, but no treatment-related lesions were observed. In this regard, metabolic acidosis and renal toxicity are the hallmarks of ethylene glycol toxicity. Both these effects arise from the metabolism of ethylene glycol to glycolic acid (acidosis) and oxalate (oxalate nephrosis). Frank renal toxicity from ethylene glycol is usually accompanied by the observation of oxalate crystals in the renal tissue and in the urine. In the Tyl (1988a) study, oxalate nephrosis was not observed. However, increased kidney weight has been observed in conjunction with oxalate nephrosis in other studies after oral exposure to ethylene glycol (DePass et al. 1986a; Woodside 1982). Since the increase in kidney weight showed a dose-response relationship and was detected in the absolute kidney weight at the mid dose, but at both absolute and relative kidney weight at the high dose, it may be assumed that the increase in kidney weight observed is related to renal toxicity. In addition, the developmental evaluation of the offspring from this study indicate a NOAEL at the mid dose and reduced fetal body weight and increased incidence of skeletal variations at the high dose. Developmental effects from ethylene glycol appear to be the result of maternal metabolic acidosis (Khera 1991). It appears that in the mouse, the maternal kidney was the most sensitive indicator of those parameters evaluated. Of the available acute inhalation studies, Tyl (1988a) had the highest NOAEL that was associated with a dose-related effect.

It is notable that the LOAEL for maternal toxicity in this study is equal to the NOAEL for developmental toxicity in this study. Effects observed in humans suggest a similar MRL. For instance, in a study by Wills et al. (1974), male volunteers experienced upper respiratory tract irritation after a 1.5minute exposure to ethylene glycol in ambient air at 55 ppm; doses above 79 ppm were not tolerated.

MRLs for intermediate-duration (15-364 days) and chronic-duration inhalation exposure (2365 days) have not been derived because suitable NOAELs or LOAELs have not been identified in the available literature. The intermediate-duration exposure inhalation study (Wills et al. 1974) did not provide enough detail on the exact exposure regimen to associate effects with concentrationsof ethylene glycol. Neither of the two chronic-duration inhalation studies (Bond et al. 1985; Triosi 1950) provided measured concentrations of exposure.

Oral MRLs

- An MRL of 2.0 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to ethylene glycol.

The MRL was based on a NOAEL of 150 mg/kg/day for developmental toxicity in mice (Tyl 1989). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans, and 10 for human variability). Timed-pregnant CD-l mice were given ethylene glycol by gavage on Gd 6-15. Females were weighed, observed daily for clinical signs, and evaluated for water intake. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, liver weight, and kidney weight. Kidneys from control and high dose dams were examined microscopically. Uterine contents were evaluated. There were no significant effects on the number of corpora lutes/dam, the number of total, nonviable, or viable implants/litter, or on sex ratio. Fetal body weights per litter were reduced only at 1,500 mg/kg/day. There was no increase in the incidence of individual or total external or visceral malformations in any group relative to the vehicle control. There was a significant increase in the incidence of two skeletal malformations (fused ribs or thora& arches) in the 1,500 mg/kg/day group, and the incidences of pooled skeletal malformations and all malformations were significantly increased in this group as well. The incidence of total malformations per litter was also significantly increased at 500 mg/kg/day. There were no significant increases in individual external or visceral variations, or in pooled external, visceral or skeletal variations or in total variations. The incidences of 23 skeletal variations were increased in the 1,500 mg/kg/day group.

One skeletal variation (bilateral extra rib 14) was also increased at 500 mg/kg/day. Other developmental studies have identified ethylene glycol as a developmental toxicant after oral administration in animals, which adversely affects the conceptus at levels that do not cause significant adverse effects in the maternal animal. In the cited study (Tyl 1989), the maternal NOAEL is 1,500 mg/kg/day, compared to a developmental NOAEL of 150 mg/kg/day. In mice, 750 mg/kg/day caused reduced litter size and increased incidence of skeletal malformations, but was a maternal NOAEL (Price et al. 1985). Neeper-Bradley (1990) detected an increase in skeletal malformations in rats treated orally with 1,000 mg/kg/day ethylene glycol on Gd 6-15, with a NOAEL for developmental effects of 500 mg/kg/day. The maternal NOAEL in that study was 2,500 mg/kg/day. Similarly, Price et al. (1985) determined a developmental LOAEL of 1,250 mg/kg/day (skeletal malformations) in rats treated orally during gestation, a dose that caused only a 17% decrease in body weight in the maternal dams. Thus, using oral exposure during the period of major organogenesis in the rodent (Gd 6-15), the developmental effects are the most sensitive end point.

An MRL for intermediate-duration oral exposure has not been derived because a suitable LOAEL or LOAEL value has not been identified in the available literature.

Intermediate-duration oral studies have found increased kidney weight and oxalate nephrosis in rats fel 1,250 and 2,500 mg/kg/day ethylene glycol, but not 625 mg/kg/day ethylene glycol for 13 weeks (Melnick 1984). In a reproductive study, decreased prenatal and postnatal viability was observed in female inice treated with 2,500 mg/kg/day ethylene glycol for 20 days and mated to male mice dosed with the same treatment level (Harris et al. 1992). No effects were seen at 700 mg/kg/day. Although either of these studies might be appropriate to use for the derivation of the MRL, the resultant value would be higher than the acute-duration oral MRL.

- An MRL of 2.0 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to ethylene glycol.

The MRL was based on a NOAEL 200 mg/kg/day for renal toxicity in rats (DePass et al. 1986a; Woodside 1982). The MRL was obtained by dividing the NOAEL value by 100 (10 for extrapolation from animals to humans and 10 for human variability). Groups of 130 male and female rats were fed diets to achieve dosage goals of 0, 40, 200, or 1,000 mg/kg/day ethylene glycol for 24 months. Mortality, body weight, diet consumption, histopathological findings, and gross findings were monitored. No evidence of oncogenicity was found. High-dose males (1,000 mg/kg/day) died prior to

the 18-month termination, with death attributable to oxalate nephrosis caused by ethylene glycol exposure. Calcium oxalate crystals were found in the urine of high-dose males and females at 12 months. Increased absolute and relative kidney weights were observed only in high-dose males at 12 months. At 12 months, high-dose males had chronic nephritis (including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis). These results were supported by hematological effects also reported in the same study. Males in the highdose group had decreases in RBC count, hematocrit, hemoglobin, and increases in neutrophils at 12 months. No effects were seen at the loier doses. Females had normal hematology. Males in the high-dose group had a 4-fold increase in BUN and creatinine at 12 months, but no changes were noted at lower dose levels. At 12 months, high-dose males showed increases in urine volume, and a reduction in urine specific gravity. The only change seen in the urinalysis of females at 12 months was a reduction in mean pH at the high-dose level. High-dose males exhibited a significant reduction in absolute and relative liver weight at 12 months. High-dose females, but not males, had mild fatty metamorphosis of the liver; organ weight was normal. Females had normal body weight gain; highdose males had decreased weight gain at 12 months of treatment. Mineralization, but no other lesions and no other organ weight changes, were seen in heart, lungs, and stomach in males, but not in females.

Other studies report similar effects. In NTP 1982, male B6C3F, mice exhibited oxalate nephrosis at 3,315 mg/kg/day, degeneration of the centrilobular hepatocytes at 1,625 mg/kg/day, and a NOAEL for hepatic effects of 812.5 mg/kg/day ethylene glycol for 2 years. In the same study, females showed hepatic and pulmonary effects at 6,500 mg/kg/day, with a NOAEL of 3,250 mg/kg/day. DePass et al. (1986a) indicates a NOAEL of 1,000 mg/kg/day for renal effects in CD-l mice after a 2-year exposure to ethylene glycol in the feed.

The EPA (IRIS 1995) assigned ethylene glycol a reference dose (RfD) of 2.0 mg/kg/day with an uncertainty factor of 100 based on a NOAEL of 200 mg/kg/day kidney toxicity in rats (DePass et al. 1986a). The chronic-duration MRL developed by the Agency for Toxic Substances and .Disease Registry for ethylene glycol is not in conflict with the current RfD for ethylene glycol.
Death.There were no reports of death from inhalation or dermal contact with ethylene glycol. Thus, contact with ethylene glycol through changing the antifreeze in an automobile, inhaling vapors from de-icing solutions, or the use of ink, paints, or other coatings is not likely to carry a significant risk of fatality. Death from ethylene glycol exposure is associated with the accidental and (more often)

intentional ingestion of ethylene glycol. The amount of ethylene glycol that can be ,accidentally ingested through normal activities (e.g., putting your fingers in your mouth, tasting an unknown liquid) is not likely to cause any adverse effects. Reports of fatalities following ingestion of ethylene glycol indicate that a volume of 150-1,500 mL (3/4-6 cups) consumed at one time may be necessary to cause death (Walton 1978). Because ethylene glycol ingestion is a common source of poisoning in domestic animals, information on fatalities in companion animals is important. Dogs and cats receiving approximately 4,000 mg/kg ethylene glycol exhibited loss of reflexes, central nervous system depression, and coma prior to death (Beckett and Shields 1971; Kersting and Nielson 1965; Penumarthy and Oehme 1975). In laboratory animals (rats, mice, monkeys) receiving a single oral dose, similar to the.scenario of an accidental or intentional ingestion of a large amount, doses in the range of 4,000 mg/kg and greater were needed to cause death (Clark et al. 1979; Richardson 1973). Administration for longer periods of time at lower doses also caused death (Blood 1965; DePass et al. 1986a; Schuler et al. 1984; Tyl et al. 1993; Woodside 1982). Monkeys given 4,000 mg/kg ethylene glycol intraperitoneally also exhibited lethal toxicity (Clay and Murphy 1977).

Systemic Effects.

Respiratory Effects. Respiratory effects occur 12-24 hours after ingestion of large amounts of ethylene glycol, and are considered to be a second stage of ethylene glycol poisoning (Vale 1979). The symptoms include hyperventilation (Godolphin et al. 1980; Gordon and Hunter 1982), shallow rapid breathing (Woolf et al. 1992; Zeiss et al. 1989) and generalized pulmonary edema with calcium oxalate crystals occasionally present in the lung parenchyma (Vale 1979). Throat and upper respiratory tract irritation was observed after inhalation exposure to 12 ppm for 20-22 hours per day for 4 weeks (Wills et al. 1974). Respiratory effects have been observed in dogs (Kersting and Nielson 1965) and mineralization of the pulmonary tissue has been observed in rats after l-year exposure to 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). Because of the low vapor potential of ethylene glycol under normal conditions, the inhalation hazard is relatively low. Persons exposed to ethylene glycol mists (airplane de-icing solutions, etc.), may experience some irritation of the respiratory tract.

Cardiovascular Effects. Cardiovascular system involvement in humans after ethylene glycol ingestion occurs at the same time as respiratory system involvement (Vale 1979). Tachycardia, ventricular gallop, and cardiac dilatation have been observed (Parry and Wallach 1974; Siew et al. 1975a; Vale

1979). As with the respiratory system response, cardiac symptoms occur after ingestion of large amounts of ethylene glycol in a short period of time. Dogs exhibited bradycardia and myocardial hemorrhages after an acute fatal oral dose of ethylene glycol (Kersting and Nielson 1965). Mineralization of the cardiac tissue was observed in rats after 1 year of treatment with 1,000 mg/kg/day ethylene glycol in the feed (DePass et al. 1986a; Woodside 1982). In general, however, it is unlikely that a low exposure to ethylene glycol would result in cardiac effects.

Gastrointestinal Effects. Very few data describing gastrointestinal effects of ethylene glycol exposure exist in the literature. Gastrointestinal tract bleeding was observed in a man after he had drunk a quart of ethylene glycol (Spillane et al. 1991). Mineralization of the stomach tissue was noted in male rats after exposure to 1,000 mg/kg/day ethylene glycol in the feed for 1 year (DePass et al. 1986a; Woodside 1982).

Hematological Eflects. The hematological system does not appear to be sensitive to ethylene glycol. Inhalation of 12 ppm ethylene glycol for 4 weeks did not alter hematological parameters in male volunteers (Wills et al. 1974). Most animal studies indicate no adverse effects on hematological parameters. Male rats treated orally with 1,000 mg/kg/day ethylene glycol for 1 year had reduced erythrocyte count, reduced hematocrit, and reduced hemoglobin (DePass et al. 1986a; Woodside 1982).

Musculoskeletal Effects. There were no *in vivo* studies on the effect of ethylene glycol on the musculoskeletal system. *In vitro* studies indicate that ethylene glycol affects myosin crossbridge formation necessary for muscle contraction (Mushtaq and Greene 1989). Data indicate that in the presence of ethylene glycol, rabbit skeletal myosin forms a more weakly binding complex than that which is observed in the absence of ethylene glycol. In addition, ethylene glycol appears to have a direct effect on actin molecules. Other studies indicate that in the presence of ethylene glycol, stretched rat muscle fibers exposed to photolysis and subsequent adenosine triphosphate (ATP) release exhibit a slower transition from the detached state to the force-producing state (Horiuti et al. 1992). These data suggest again that ethylene glycol affects aspects of muscle fiber crossbridge .formation (Horiuti et al. 1992). Similar results were reported after calcium-induced release of ATP from rat muscle fibers in the presence of ethylene glycol (Sakoda and Hiruiti 1992). The relevance of these musculoskeletal effects to human exposure to ethylene glycol is not clear.

Hepatic Effects. Hepatic involvement in ethylene glycol toxicity is not evident in reports of human poisoning. In general, laboratory animals do not exhibit marked adverse hepatic effects, after acute or intermediate exposure (Harris et al. 1992; Hong et al. 1988; Neeper-Bradley 1990; Price et al. 1985; Tyl 1985, 1988a; Tyl et al. 1993). Degeneration of the centrilobular hepatocytes was observed in male mice fed 6,500 mgfkglday for up to 13 weeks, whereas fatty degeneration of the liver was seen in female rats fed 200 mg/kg/day ethylene glycol for 2 years (DePass et al. 1986a; Melnick 1984; NTP 1992). Therefore, the liver may not be a sensitive indicator of ethylene glycol exposure, especially after acute exposure.

Renal Effects. Adverse renal effects have been observed in the third stage of human ethylene glycol poisoning, which occurs 24-72 hours after acute exposure. The hallmark of renal toxicity is the presence of calcium oxalate monohydrate crystals in the renal tubules, and their presence in the urine after ingestion of large amounts of ethylene glycol (Blakeley et al. 1993; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980). Focal tubular degeneration, atrophy, and tubular interstitial inflammation have also been observed (Factor and Lava 1987). Renal damage, if untreated, can lead to renal failure (Chung and Tuso 1989; Gordon and Hunter 1982; Jacobson et al. 1984; Mallya et al. 1986). With therapy, however, normal or near normal renal function can be restored. Similar renal damage has been observed in companion animals and in laboratory animals, primarily after acute exposure to high doses or intermediate or chronic exposure to lower doses (Beckett and Shields 1971; DePass et al. 1986a; Grauer et al. 1987; Melnick 1984; NTP 1992; Penumarthy and Oehme 1975; Roberts and Siebold 1969; Woodside 1982).

Body Weight Effects. Body weight does not appear to be a sensitive indicator of ethylene glycol toxicity. There were no reports of changes in body weight after ethylene glycol exposure in humans. In animals, a similar lack of effect has been observed after acute exposure. Male rats exhibit decreased body weight after exposure to 2,500 mg/kg/day ethylene glycol in the feed for 13 weeks, or 1,000 mg/kg/day in the feed for 1 year (DePass et al. 1986a; Melnick 1984; Woodside 1982). Mice exhibited decreased body weight after 1,625 mgfkg/day in the feed for 13 weeks, but no ,effect after 1,000 mg/kg/day in the feed for 2 years (DePass et al. 1986a; NTP 1992).

Metabolic Effects. One of the major adverse effects following acute oral exposure of humans to ethylene glycol is metabolic acidosis (Berger and Ayzar 1981; Blakeley et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Gordon and Hunter 1982: Heckerling 1987; Jacobsen et al. 1988). Data

indicate that glycolic acid, a metabolite of ethylene glycol, is responsible for causing metabolic acidosis and accompanying ethylene glycol toxicity (Jacobsen et al. 1984). Similar observations have been made in animals (Clay and Murphy 1977; Hewlett et al. 1989; Marshall 1982).

Immunological and Lymphoreticular Effects. Ethylene glycol does not seem to have any characteristic adverse immunological effects. There were no studies that specifically addressed immunological effects in humans or animals. Data in the literature are sparse and conflicting (DePass et al. 1986a; Spillane et al. 1991; Underwood and Bennett 1973; Wills et al. 1974; Woodside 1982). Thus, it appears unlikely that ethylene glycol exposure will cause significant immunological effects.

Neurological Effects. Few data are available describing neurological effects of dermal or inhalation ethylene glycol exposure. The data that are available indicate that acute oral intoxication is the source of the most characteristic neurological manifestations. Specifically, adverse neurological reactions are among the first symptoms to appear in human ethylene glycol poisoning. These are the only symptoms that are attributable directly to ethylene glycol, and resemble ethanol intoxication. They occur within 30 minutes to 12 hours after exposure, and include ataxia, disorientation, restlessness, slurred speech, and somnolence, progressing to convulsions and coma (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Robinson and McCoy 1989; Vale 1979; Woolf et al. 1992). These symptoms may be ameliorated by supportive therapy. Some evidence exists that damage to the cranial nerves may occur much later in the toxic process, especially if supportive therapy is delayed (Chung and Tuso 1989; Factor and Lava 1987; Mallya et al. 1986; Spillane et al. 1991). Similar effects have been seen in laboratory animals after large oral doses of ethylene glycol were administered (Beckett and Shields 1971; Clark et al. 1979; Penumarthy and Oehme 1975).

In vitro studies of the effect of ethylene glycol on nerve cell cultures from Wistar rats indicate that ethylene glycol caused neuronal degeneration, decreased in acetylcholinesterase-containing cells, and reactive cellular grouping (Capo et al. 1993).

Reproductive Effects. Studies have not addressed the reproductive toxicity of ethylene glycol in humans. Mice treated with 200 mg/kg/day ethylene glycol showed some degeneration of the seminiferous tubules (Hong et al. 1988). In addition, female mice orally exposed to 2,500 mg/kg/day ethylene glycol for 20 days, and mated on the eighth day of exposure with males that had been treated for 17 days prior to mating, had fewer live litters, more dead implants, and more litters totally

resorbed (Harris et al. 1992). However, male mice showed no direct effects on the reproductive system, suggesting that the effects originated with the female (Harris et al. 1992). Most other studies indicate no direct adverse effects of ethylene glycol on the reproductive organs (Depass et al. 1986a; Nagano et al. 1984).

Developmental Effects. Studies have not addressed the developmental toxicity of ethylene glycol in humans. Female mice and rats exhibit adverse effects on developmental parameters after exposure to ethylene glycol during gestation at doses of 2,100-2,500 ppm, and 400 ppm, respectively, by noseonly inhalation (Tyl 1988a), and 500 and 750 mg/kg/day, respectively, by gavage (Price et al. 1985; Tyl 1989). Rabbits receiving 2,000 mg/kg/day ethylene glycol by gavage showed no adverse developmental effects (Tyl et al. 1993). No effects were seen after dermal exposure of mice to doses up to 3,549 mg/kg (Tyl 1988b). Thus, inhalation or oral exposure during organogenesis to relatively large doses of ethylene glycol may adversely affect the developmental process. However, evidence exists in laboratory studies that these adverse effects can be eliminated by correcting the metabolic acidosis that accompanies ethylene glycol exposure (Khera 1991) (see Section 2.7). Thus, the developmental effects of ethylene glycol poisoning may be preventable with proper supportive therapy.

In vitro studies of rat embryo development indicate that ethylene glycol is embryotoxic (Grafton and Hansen 1987). Ethylene glycol added to culture medium decreased the morphological score, somite number, crown-rump length, and head length, as well as DNA and protein content of rat embryos. Absence of yolk sac circulation, absent hindlimb bud, hypoplastic telencephalon, and lack of development of the otic and optic systems were also seen in exposed embryos.

Genotoxic Effects. Studies in humans have not addressed the genotoxic effects of ethylene glycol. However, in both *in vivo* and *in vitro* laboratory studies, ethylene glycol is negative for genotoxic effects. In Fischer 344 rats that received oral doses of 40, 200, and 1,000 mg/kg/day for three generations, there were no dominant lethal mutations (DePass et al. 1986b). The *in vitro* mutagenicity studies in *Salmonella typhimurium* gave uniformly negative results (Clark let al. 1979; McCann et al. 1975; Pfeiffer and Dunkelberg 1980; Zeiger et al. 1987). No growth inhibition due to DNA damage by ethylene glycol was observed in a battery of *Escherichia coli* repair-deficient strains (McCarroll et al. 1981). Negative results were also obtained in two sets of studies when ethylene glycol was tested for gene mutation in the yeast, *Schizosaccharomyces pombe* (Abbondandolo et al. 1980), and for aneuploidy induction in the fungus, *Neurospora crassa* (Griffiths 1979, 1981). Because

of the information available in in vitro culture and animals, it is reasonable to conclude that exposure to ethylene glycol poses minimal risk of causing genotoxic effects in exposed persons. A summary of genotoxic data for ethylene glycol is presented in Tables 2-7 and 2-8.

It is reasonable to assume, therefore, that ethylene glycol poses little risk of genotoxicity.

Cancer. Studies in both humans and animals indicate that there is little carcinogenic risk after ethylene glycol exposure, although the data are scanty (Bond et al. 1985; DePass et al. 1984, 1986a; NTP 1992; Woodside 1982).

The National Toxicology Program (NTP) has not classified ethylene glycol as a carcinogen. The EPA (IRIS 1995) has not assigned ethylene glycol a weight-of-evidence classification.

Minimal Risk Levels for Propylene Glycol

Inhalation MRLs

No MRLs for acute- or chronic-duration inhalation exposure to propylene glycol were derived because data are insufficient. Only one acute-duration inhalation exposure study was found in the available literature, in which rabbits were exposed to only one dose (10% aerosol) of propylene glycol for 20 and ‘120 minutes (Konradova et al. 1978). An increased number of degenerated goblet cells in the tracheal lining was observed at both doses. Only a single study was found in the available literature for inhalation exposure to propylene glycol for chronic-duration (Robertson et al. 1947) exposure. This study did not provided enough information from which to derive an MRL.

- An MRL of 0.009 ppm has been derived for intermediate-duration (15-364 days) inhalation exposure to propylene glycol.

The MRL was based on the LOAEL of 51 ppm for nasal hemorrhaging in rats (Suber et’al. 1989). The MRL was obtained by dividing the LOAEL value by 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) and multiplying by factors to adjust the exposure from 6 hours per day (6 or 24) and 5 days per week (5 of 7) to continuous exposure. Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by

Table 2-7. Genotoxicity of Ethylene Glycol *In Vivo*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat (*in utero* exposure)	Dominant lethal	NA	–	DePass et al. 1986b

– = negative result; NA= not applicable

Table 2-8. Genotoxicity of Ethylene Glycol *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Clark et al. 1979
	Gene mutation	–	–	McCann et al. 1975
	Gene mutation	–	–	Pfeiffer and Dunkelberg 1980
	Gene mutation	–	–	Zeiger et al. 1987
Escherichia coli	DNA damage	–	–	McCarroll et al. 1981
Eukaryotic organisms:				
Schizosaccharomyces pombe	Gene mutation	–	–	Abbondandolo et al. 1980
	Aneuploidy induction	–	–	Griffiths 1979, 1981
Neurospora crassa		No data	–	Griffiths 1979, 1981

– = negative result

nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2 to 14, the average of nasal hemorrhaging in male rats was <1, 64, 74, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were <1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5-7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption. beginning on study days 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was' observed in male rats treated with high dose (707 ppm) of propylene glycol while females treated with a medium dose (321 ppm) of propylene glycol had an increase in total serum protein. These changes were considered to be sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Oral MRLs

No MRLs for acute-, intermediate-, or chronic-duration oral exposure to propylene glycol were derived because data are insufficient.

Death.There were no reports in the literature of human death due to propylene glycol exposure by any route, at any level, for any length of time. Lethal oral doses for rats, mice, and guinea pigs range from 8,000 to 46,000 mg/kg (Clark et al. 1979; EPA 1987a). Monkeys died after inhalation exposure to 112 ppm propylene glycol after 13 months (Robertson et al. 1947). It is unlikely that sufficient amounts of propylene glycol would be inhaled, ingested, or absorbed through the skin to be fatal.

Systemic Effects.

Respiratory Effects. Acute respiratory arrest was observed in an 8-month-old infant being treated for second and third degree bums with an topical antibiotic formulation containing propylene glycol (Fligner et al. 1985). The contribution of the bum injury and the antibiotic therapy to the respiratory arrest, however, is not known. Anecdotal accounts of respiratory irritation after exposure to propylene glycol as a mist or vapor in theatrical productions was found in the literature (Ross01 1990). Studies of laboratory animals are inconclusive with respect to the respiratory effects of propylene glycol (Konradova et al. 1978; Suber et al. 1989).

Cardiovascular Effects. Very limited information is available in humans and animals on cardiovascular effects after exposure to propylene glycol. In the case of the 8-month-old infant mentioned above, cardiac arrest accompanied the respiratory arrest (Fligner et al. 1985). The contribution of the infant's injuries to the observed symptoms is not known. No cardiovascular effects were noted in rats after 2 years of exposure to oral doses of propylene glycol up to 49,500 ppm (Morris et al. 1942). Myocardial edema was observed in a horse prior to death from an accidental oral administration of 7,904 mg/kg propylene glycol (Dorman and Haschek 1991).

Gastrointestinal Effects. There were no reports of the effects of propylene glycol on the gastrointestinal system of humans. Propylene glycol is approved as a direct food additive. Toxicity to the gastrointestinal system has been shown to be negligible. In rats, only a very large oral dose of 23,500 mg/kg caused hemorrhagic enteritis (Clark et al. 1979). Monkeys and rats exposed by inhalation to concentrations of propylene glycol up to 112 ppm for 13-18 months had no gastrointestinal effects (Robertson et al. 1947). The effect of orally administered propylene glycol on the brush border membrane from the jejuno-ileum portion of the intestines of rats was investigated *in vivo* and *in vitro* (Morshed et al. 1991a). In rats receiving 2,942 mg/kg propylene glycol for lo-30 days, brush border enzymes including sucrase, lactase, and gamma-glutamyl transpeptidase

exhibited a tendency toward increased activity. Absorption of D-glucose and calcium was increased after 10 days of treatment, whereas absorption of D-glucose, glycine, L-aspartic acid, L-lysine, and calcium were elevated after 20 or 30 days of treatment. The structural integrity of the jejunal surface was not adversely affected. When evaluated in vitro, propylene glycol inhibited sucrase, lactase, and maltase, in a non-competitive dose-related manner, with sucrase being the most affected. Nutrient transport was not altered. These studies suggest that ingested propylene glycol may influence intestinal digestive and absorptive functions, and that the *in vivo* and *in vitro* effects are through different mechanisms.

Hematological Effects. Propylene glycol does not appear to adversely affect hematological parameters in humans (Lolin et al. 1988). In animals, however, intermediate- and chronic-duration exposure to propylene glycol may lead to hemolysis of red blood cells. For example, propylene glycol is used as a moistening agent in cat food. Studies of cats fed 1,200 mgkglday and higher doses of propylene glycol for 2-17 weeks exhibited hypocellularity of the bone marrow, increased Heinz body formation and decreased RBC survival (Christopher et al. 1989a; Weiss et al. 1990, 1992). Similar results were seen in dogs after chronic exposure to 5,000 mg/kg/day (Weil et al. 1971).

Musculoskeletal Effects. No *in vivo* data on musculoskeletal effects of propylene glycol were found in the literature. Propylene glycol was shown to cause damage with subsequent creatine kinase release from rat skeletal muscle (Brazeau and Fung 1990). Attempts to elucidate the mechanism of this damage suggested that propylene glycol-mediated damage of skeletal muscle may be caused by an intracellular mechanism rather than by a direct action on the sarcolernma, and that the mechanism may involve calcium. Frog muscle preparations exhibit increased twitch tension in the presence of propylene glycol (Hattori and Maehashi 1993). Propylene glycol appears to facilitate transmitter release from the nerve terminals and raise the acetylcholine sensitivity of the muscle endplate.

Renal Effects. No *in vivo* studies describing frank renal toxicity for propylene glycol alone were found (Christopher et al. 1989a; Gaunt et al. 1972; Robertson et al. 1947; Suber et al. 1989). Polyuria and polydipsia have been observed in cats ingesting 8,000 mg/kg/day propylene glycol for 3 or more weeks (Christopher et al. 1989a, 1990b). Propylene glycol has been shown to damage the membranes of human proximal tubule cells in culture (Morshed et al. 1994). Lactate release was increased and glucose accumulation decreased in human proximal tubule cells prior to observation of membrane

damage, indicating that damage was occurring even when the plasma membrane appeared to be unaffected.

Dermal Effects. Propylene glycol has few irritative properties in humans when applied topically, except in the case of unusual sensitivity (Aberer et al. 1993; Corrazza et al. 1993; Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Trancik and Maibach 1982; Warshaw and Herrmann 1952; Willis et al. 1989).

Body Weight Efsects. Propylene glycol has little effect on body weight. Exposure of rhesus monkeys to 112 ppm propylene glycol by inhalation for up to 13 months had no effect on body weight, whereas in the same study, rats treated to the same dose for 18 months exhibited a 50% decrease in body weight (Robertson et al. 1947). In another study, rats exposed to 321 ppm for an intermediate period of time had decreased body weight (Suber et al. 1989).

Metabolic Effects. Like ethylene glycol, propylene glycol causes acidosis, through conversion to lactic and pyruvic acids. However, the acidosis from propylene glycol is not as severe as that caused by ethylene glycol. Evidence of this comes from clinical cases of dermal or intravenous treatment with drug formulations containing propylene glycol (Fligner et al. 1985; Glasgow et al. 1983; Huggon et al. 1990; Kelner and Bailey 1985). Acidosis also occurs after ingestion of large amounts of propylene glycol (Lolin et al. 1988). Increased osmolal gap was observed in cats after ingestion of 1,600 mg/kg/day propylene glycol for 5 weeks (Christopher et al. 1990b). It seems possible that metabolic acidosis could develop in humans after exposure to large doses.

High levels of propylene glycol in the plasma can lead to an increase in the osmolal gap. Propylene glycol is oxidatively converted to lactic and pyruvic acids which, if present in sufficient amounts, contribute to a metabolic acidosis. However, acidosis from propylene glycol is not as severe as that due to ethylene glycol. An 8-month-old infant with a severe burn was topically treated with 9,000 mg/kg/day of propylene glycol used as a vehicle for silver sulfadiazine (Fligner et al. 1985). The osmolal gap reached a maximum of 130 milliosmoles/kg 14 days after the treatment started, while serum propylene glycol level peaked at 1,059 mg/dL. Due to the high dose of propylene glycol, and the possible concomitant effects of both the bum injury and the sulfadiazine therapy, the actual source of the metabolic effect in this infant could not be determined, although propylene glycol can not be ruled out as the causative agent. The bum injury may have contributed to the increased absorption of

propylene glycol and hence, the hyperosmolality. Another infant developed increased osmolality after being exposed intravenously to propylene glycol (2.4 mg/kg) used as a vehicle for Enoximone (Huggon et al. 1990). However, in another study of acute dermal propylene glycol exposure of 12 adults to 6,100 mg/kg/day for 5 days, propylene glycol had no effect on either serum osmolality or lactic acid levels (Commens 1990). Increased serum propylene glycol levels, increased lactate, and increased total acid (serum lactate and pyruvate) were also found in a retrospective study of 35 human sera samples and 8 cerebrospinal fluid samples from patients receiving intravenous medications with propylene glycol as the vehicle (Kehrer and Bailey 1985). The daily dose of propylene glycol ranged from 57 to 771 mg/kg. None of the sera samples were specifically collected for determination of propylene glycol levels; therefore, the time between propylene glycol administration and serum collection varied and was not specified in the report. However, statistically significant correlation was found between the lactate levels in serum and cerebrospinal fluid samples and the corresponding propylene glycol concentrations (Kelner and Bailey 1985). Although the results of these studies are not conclusive, it seems that increased lactate levels leading to acidosis and increased osmolality may develop in humans in the event high levels of propylene glycol are absorbed into the blood stream.

Immunological and Lymphoreticular Effects. Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Tranick and Maibach 1982) the irritative properties of propylene glycol are minimal and can not be classified as allergic reactions (Aberer et al. 1993; Hannuksela and Forstrom 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989).

Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells in vitro (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties, and should be evaluated in light of this information.

Neurological Effects. Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including

stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979), and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity.

Reproductive Effects. Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment as high as 10,000 mg/kg/day during gestation, or inhalation exposure to 112 ppm for 18 months (Kavlock et al. 1987; NTP 1985; Robertson et al. 1947).

Developmental Effects. Specific *in vivo* studies have not addressed the developmental toxicity of propylene glycol in humans or animals. *In vitro* studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development.

Genotoxic Effects. Studies in humans or animals have not addressed whether adverse genotoxic effects occur after ***in vivo*** exposure to propylene glycol. Propylene glycol was not mutagenic in S. *typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). Propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). A summary of genotoxic data for propylene glycol is presented in Table 2-9.

Cancer. There is no evidence that propylene glycol is carcinogenic in humans or animals.

The National Toxicology Program (NTP) has not classified propylene glycol as a carcinogen. The EPA (IRIS 1995) has not assigned propylene glycol a weight-of-evidence classification.

Table 2-9. Genotoxicity of Propylene Glycol *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Clark et al. 1979
	Gene mutation	–	–	Pfeiffer and Dunkelberg 1980
Mammalian cells:				
Human fibroblasts	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster cells	Chromosome aberrations	–	–	Sasaki et al. 1980
Chinese hamster lung cells	DNA damage	–	–	Swenberg et al. 1976

– = negative result

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. Ihey have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). Biomarkers of exposure have been used by industrial hygienists in limited instances as evidence of exposure to certain chemicals. The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethylene glycol and propylene glycol are discussed in Section 2.4.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect have been used by clinicians to guide them in diagnoses and treatment. Biomarkers of effects caused by ethylene glycol and propylene glycol are discussed in Section 2.4.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. Biomarkers of susceptibility may be defined, for all practical purposes, as the susceptibility of the individual, relative to its own population. If biomarkers of susceptibility exist, they are discussed in Section 2.6, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Ethylene Glycol oy Propylene Glycol

Biomarkers of exposure to a compound are of use only if they are specific to the compound in question. The biomarkers for ethylene glycol meet this criterion. Exposure to ethylene glycol can be measured by determining the levels of ethylene glycol in the blood. There are two difficulties associated with determining blood levels of ethylene glycol. The first is that ethylene glycol is absorbed and metabolized fairly rapidly in the body, which means that in most cases it is not present in the blood for more than a few hours after exposure. Second, the complex procedure needed for determination of the ethylene glycol is not always readily available in emergency situations.

Presence of ethylene glycol in the blood would indicate a very recent exposure. In humans, ethylene glycol has a relatively short half-life in the body (about 3-4 hours) (Winek et al. 1978), and thus, only exposures that occurred 10-20 hours earlier would be detected in the blood. Ethylene glycol concentrations in urine are higher than ethylene glycol concentrations in serum, and thus, remain detectable for a longer period. Rapid methods for determining ethylene glycol in serum and urine are available for use in the clinical setting (Aarstad et al, 1993; Blandford and Desjardins 1994). The information on ethylene glycol levels in bodily fluids has been scarce until recently because gas chromatography, which is most often used for ethylene glycol determination (see Chapter 6 for details), has not always been available to an emergency department physician. In general, ethylene glycol blood levels show no direct correlation with degree of toxicity (Jacobsen and McMartin 1986). Values in case reports have varied from 14.5 mg/dL (Underwood and Bennett 1973) to 650 mg/dL (Peterson et al. 1981). The great variation results from differences in the amounts of ethylene glycol consumed and in the time delays between ingestion and blood sampling (Jacobsen and McMartin 1986; Peterson et al. 1981; Rothman et al. 1986; Underwood and Bennett 1973; Walton 1978).

Because ethylene glycol is rapidly absorbed and biotransformed in the body, some of its metabolic products may be used to identify exposure to ethylene glycol. Metabolic acidosis due to increased amounts of glycolic acid and lactic acid occurs in cases of intoxication with ethylene glycol (Jacobsen et al. 1984). However, lactic acid is not a specific marker for ethylene glycol exposure, and thus, has no use as a biomarker in this instance. In cases of exposure to ethylene glycol, there is a small increase in the amount of oxalic acid in blood, contributing to metabolic acidosis. As oxalic acid interacts with calcium from the body, it forms calcium oxalate crystals which can be detected in the urine (Jacobsen et al. 1988). Accumulation of glycolic acid primarily accounts for the acidosis of ethylene glycol intoxication; its presence can indicate significant exposure, even when the ethylene glycol blood levels are very low (Hewlett et al. 1986; Jacobsen et al. 1984). Glycolic acid can be used as a relatively sensitive indicator of ethylene glycol exposure, due to its relatively high production from ethylene glycol and its rapid clearance from the body. Rapid and accurate methods of analysis now exist for glycolic acid in serum (Fraser and MacNeil 1993). Calcium oxalate is a less sensitive marker, due to its slow formation and its relatively slow clearance from the body. Both serum glycolic acid and urinary calcium oxalate have been used to identify exposure to ethylene glycol.

Propylene glycol can also be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed.

2.5.2 Biomarkers Used to Characterize Effects Caused by Ethylene Glycol or Propylene Glycol

Adverse neurological reactions that can culminate in convulsions and coma are among the first symptoms in humans after ethylene glycol intoxication (Zeiss et al. 1989). Some of the most common manifestations of ethylene glycol neurotoxicity include ataxia, slurred speech, semiconsciousness, unresponsiveness, and somnolence (Anonymous 1987; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Parry and Wallach 1974; Rothman et al. 1986; Spiilane et al. 1991; Underwood and Bennett 1973). Several more recent studies described adverse effects of ethylene glycol on cranial nerves; the symptoms appear later and may involve facial paralysis, bilateral optic nerve dysfunction, and peripheral neurosensory hearing loss. These symptoms are not specific to ethylene glycol, but in conjunction with known or suspected exposure, may serve to guide diagnosis and treatment.

2. HEALTH EFFECTS

The presence of calcium oxalate monohydrate crystals is the hallmark of ethylene glycol intoxication. The crystals can be deposited in renal tubules and/or excreted in urine after exposure to relatively large amounts of ethylene glycol (Anonymous 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al. 1975a; Underwood and Bennett 1973). In some cases, there is only a brief period of calcium oxalate dihydrate crystalluria (Jacobsen et al. 1988). Renal toxicity can also be indicated by increased serum levels of BUN or creatinine; however, this occurs relatively late in intoxication (i.e., stage 3, 48-72 hours after ethylene glycol ingestion) and is not specific for ethylene glycol intoxication (Grauer et al. 1987).

Respiratory system involvement occurs 12-24 hours after ingestion of ethylene glycol. The symptoms include hyperventilation (Godolphin et al. 1980), shallow rapid breathing (Zeiss et al. 1989), and generalized pulmonary edema (Vale 1979).

Cardiovascular system involvement occurs during the second phase of ethylene glycol poisoning, at the same time as the respiratory system involvement. The symptoms are tachycardia, ventricular gallop, and ventricular dilation (Parry and Wallach 1974; Siew et al. 1975a; Vale 1979). As in the case of respiratory effects, cardiovascular involvement occurs after exposure to relatively high oral levels of ethylene glycol. Both of these types of effects are not specific to ethylene glycol intoxication.

Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content.

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.6 INTERACTIONS WITH OTHER CHEMICALS

Information regarding the influence of other chemicals on the toxicity of ethylene glycol comes from case studies describing treatment after accidental or intentional ingestion of ethylene glycol. The toxic effects of ethylene glycol result from its metabolic conversion by alcohol dehydrogenase into glycolic

acid which is further metabolized to oxalate. The formation of oxalate crystals is associated with renal toxicity encountered after exposure to ethylene glycol. Administration of ethanol, 4-methyl pyrazole (also used as antidotes in cases of methanol poisoning), or 1,3-butanediol reduces or eliminates ethylene glycol toxicity. This is accomplished by the following mechanisms: 1) ethanol, which is also metabolized by alcohol dehydrogenase, competes with ethylene glycol for the enzyme, thus preventing the formation of potentially toxic ethylene glycol metabolites; 2) 4-methyl pyrazole inhibits the activity of alcohol dehydrogenase (Baud et al. 1987, 1988); and 3) 1,3-butanediol is also a competitive inhibitor of ethylene glycol biotransformation and reduces the formation of glycolic acid (Hewlett et al. 1983). Therefore, ethanol, 4-methyl pyrazole, and 1,3-butanediol reduce the toxicity of ethylene glycol by interacting with or inhibiting the activity of alcohol dehydrogenase, thus reducing the amount of glycolic acid and oxalate formed.

Magnesium and vitamin B6 were found to affect the toxicity of ethylene glycol in animals. In rats, vitamin B6 accelerates the oxidation of glyoxylate to carbon dioxide rather than to oxalate (Gershoff and Audrus 1962). Vitamin B6 deficiency can cause inhibition of ethylene glycol's oxidation to carbon dioxide and, thus cause an increase in ethylene glycol toxicky. Magnesium may prevent renal deposition of calcium oxalate by altering solvent characteristics of oxalate in urine (Browning 1965; Gershoff and Andrns 1962; Khan et al. 1993).

Ethylene glycol has been shown to be a substrate for rat liver microsomal cytochrome P-450 *in vitro* (Kukielka and Cederbaum 1991). If such activity were to occur *in vim,* ethylene glycol may interact with the metabolism of many drugs that would be substrates for the same enzyme.

In the first step of biotransformation, propylene glycol is catalyzed by alcohol dehydrogenase, as in the case of ethylene glycol. 4-Methyl pyrazole is an inhibitor of propylene glycol metabolism (Morshed et al. 1988). As in the case of ethylene glycol, 4-methyl pyrazole may reduce potential toxic effects of propylene glycol and act as an antidote by interfering with the biodegradation of propylene glycol.

Review of the literature regarding the interaction and influence of other chemicals on the toxicity of propylene glycol revealed that propylene glycol is often used as a vehicle for administration of certain medications such as Valium, Dilantin, Nembutal (Kemer and Bailey 1985), dihydrotachysterol (DHT) (Arulanantham and Gene1 1978), Ketoconazo1e.crean.r (Eun and Kim 1989), and Enoximone (Huggon et al. 1990). Among the observed effects were seizures and cerebral irritability (DHT), increased

serum lactate (Valium, Dilantin, and Nembutal), increased serum osmolality (Enoximone), and skin allergy (Ketoconazole cream). All these adverse effects are attributed to propylene glycol and associated with the prolonged administration of these medications using propylene glycol as the vehicle. However, the precise interaction between propylene glycol and these medications was not investigated.

In rats, hexobarbital-induced sleeping time was prolonged in the presence of propylene glycol (Dean and Stock 1974), probably because of competition for drug-metabolizing enzymes. Studies in rabbits have shown that propylene glycol inhibited the elimination of 8-chlorotheophylline and dimenhydrinate from the blood, due to a diminished metabolism of the two drugs (Walters et al. 1993).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to ethylene glycol and propylene glycol compared to most persons exposed to the same level of ethylene glycol and propylene glycol in the environment. Reasons include genetic makeup, developmental stage, health and nutritional status, and chemical exposure history. These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or compromised function of target organs. For these reasons, the elderly with declining organ function, people with unusual chemical exposure history, heavy users of alcohol, and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Because of its sweet taste, easy access, and frequent improper storage and disposal, ethylene glycol may present a particular hazard to small children. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

The review of literature regarding toxic effects of ethylene glycol revealed that individuals deficient in vitamin B6 may be more sensitive to toxic effects of ethylene glycol because vitamin-B6 may reduce the accumulation of toxic metabolites (Browning 1965; Gershoff and Andrus 1962). Similarly, magnesium deficiency appears to encourage calcium oxalate deposition in the renal tubules, especially in the presence of high calcium levels (Ebisuno et al. 1987). Thus, individuals who are deficient in magnesium and/or ingest high levels of calcium may be more sensitive to the toxic effects of ethylene glycol.

No information was found on populations with unusual sensitivity to propylene glycol. However, populations that may show increased sensitivity include very young children, who have immature hepatic detoxification systems, and individuals with impaired liver or kidney function. Studies of burn patients indicate the absorption of propylene glycol from antibiotic preparations can be correlated with total bum surface area and the severity of the bum (Kulick et al. 1985). Thus, bum patients may be at a higher risk for possible adverse effects of propylene glycol. In addition, propylene glycol has been found in the blood of alcoholics with cirrhosis of the liver, in the absence of measurable blood alcohol (Casazza et al. 1987). Thus, alcoholics with liver disease may comprise a population that is unusually susceptible to the effects of propylene glycol.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

2.8.1 Reducing Peak Absorption Following Exposure

No studies were found describing methods to reduce peak absorption of ethylene glycol after inhalation exposure. After oral exposure, gastric lavage or charcoal absorption can be helpful in reducing absorption. Dermal absorption can be minimized through washing the skin with soap to remove any existing ethylene glycol.

No studies on reducing peak absorption of propylene glycol after inhalation exposure were found. The pharmacokinetic properties of propylene glycol are not completely understood, but absorption from the gastrointestinal tract after oral exposure is fairly rapid. The maximum plasma concentration of propylene glycol in humans is reached within 1 hour after oral exposure, while the elimination half-life is about 4 hours. The total body clearance is about 0.1 L/kg/hour and seems to be serumconcentration dependent (Yu et al. 1985). Dose-dependent elimination is seen in rats, with saturation of the pathways at doses above 5,880 mg/kg (Morshed et al. 1988). However, no studies on reducing peak absorption following oral exposure were found.

Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

2.8.2 Reducing Body Burden

Methods for reducing the body burden of ethylene glycol after oral exposure include hemodialysis (Parry and Wallach 1974). No data describing methods of reducing the body burden of ethylene glycol after inhalation or dermal exposure were found, although it would seem that the hemodialysis would also work in these instances.

No methods for reducing the body burden of propylene glycol after inhalation, oral, or dermal exposure were found.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Metabolic acidosis is a common symptom of ethylene glycol toxicity. The primary therapies are aimed at this toxic effect. Clinical case histories from accidental and intentional ingestion of ethylene glycol show that metabolic acidosis can be controlled and eliminated. Administration of bicarbonate to correct the blood pH, and ethanol to compete for the enzymes that convert ethylene glycol to glycolic acid, can prevent any sequelae of ethylene glycol poisoning if administered early enough. Fluid therapy and volume expansion, and diuresis are also important treatments for ethylene glycol poisoning. Peritoneal and hemodialysis are useful therapies for reducing the toxic effects of ethylene glycol. In laboratory studies, Khera (1991) has shown that in rats, correction with bicarbonate of metabolic acidosis caused by ethylene glycol administration (up to 5,000 mg/kg orally on Gd 11) reduced or prevented subsequent developmental anomalies. Thus, proven methods of reducing the toxic effects of ethylene glycol exist and can be used in the event of a toxic exposure.

Male Porton rats receiving 999-1,110 mg/kg ethylene glycol in the drinking water for 21 days exhibited significantly increased renal calcium oxalate deposition when given diets supplemented with 30 or 60% sucrose (Rofe et al. 1986). The authors hypothesized that the increased levels of sugar or sugar alcohol as a result in increased carbohydrates in the diet, increase the supply of calcium in the renal medulla, leading to increased calcium oxalate deposition. The increased supply of calcium may be the result of decreased reabsorption in the tubules, or increased release due to increased energy supply from the carbohydrate metabolism. This study suggests that administering a diet low in carbohydrates may be helpful in reducing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Magnesium and vitamin B6 were found to affect the toxicity of ethylene glycol in animals. In rats, vitamin B6 accelerates the oxidation of glyoxylate to carbon dioxide rather than to oxalate (Gershoff and Andrus 1962). Vitamin B6 deficiency can cause inhibition of ethylene glycol's oxidation to carbon dioxide and, thus cause an increase in ethylene glycol toxicity. Magnesium may prevent renal deposition of calcium oxalate by altering solvent characteristics of oxalate in urine (Browning 1965; Gershoff and Andrus 1962; Khan et al. 1993). Magnesium deficiency, especially in the presence of increased calcium intake, has been shown to accelerate renal tubular calcium oxalate deposition (Ebisuno et al. 1987). Thus, administration of magnesium may aid in preventing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Renal calcium oxalate deposition in rats after ethylene glycol exposure has been shown to increase in the presence of high levels of dietary calcium (Ebisuno et al. 1987). Administration of phytin or citrate appears to inhibit calcium oxalate deposition in the renal tubules. Thus, phytin or citrate may be a useful dietary agent for the prevention of adverse renal effects after ethylene glycol ingestion, especially in the presence of high calcium levels.

4-Methyl pyrazole, an alcohol dehydrogenase inhibitor, effectively blocks the metabolism of ethylene glycol to toxic intermediates and has been shown to be effective in preventing renal effect of ethylene glycol after ingestion (Baud et al. 1987, 1988; Dial et al. 1989, 1994). Thus, administration of 4-methyl pyrazole may be an effective treatment for preventing renal failure after ethylene glycol exposure.

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hammksela and Forstrijm 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since, however, it does cause metabolic acidosis, albeit to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylene glycol and propylene glycol is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylene glycol and propylene glycol.

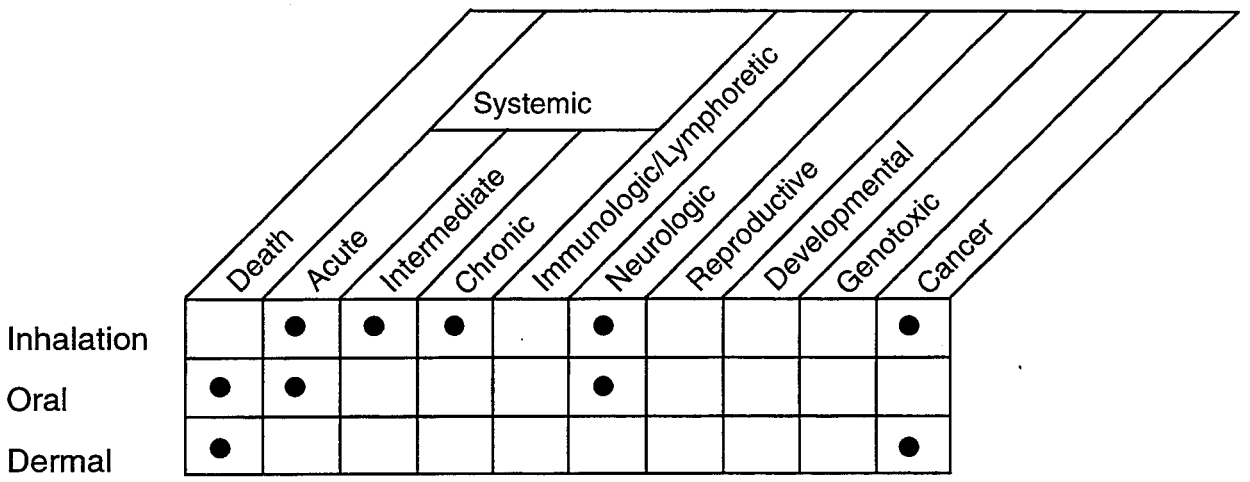
The following categories of possible data needs have been identified by scientists from ATSDR. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be fulfilled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be prepared.

2.9.1 Existing Information on Health Effects of Ethylene Glycol and Propylene Glycol

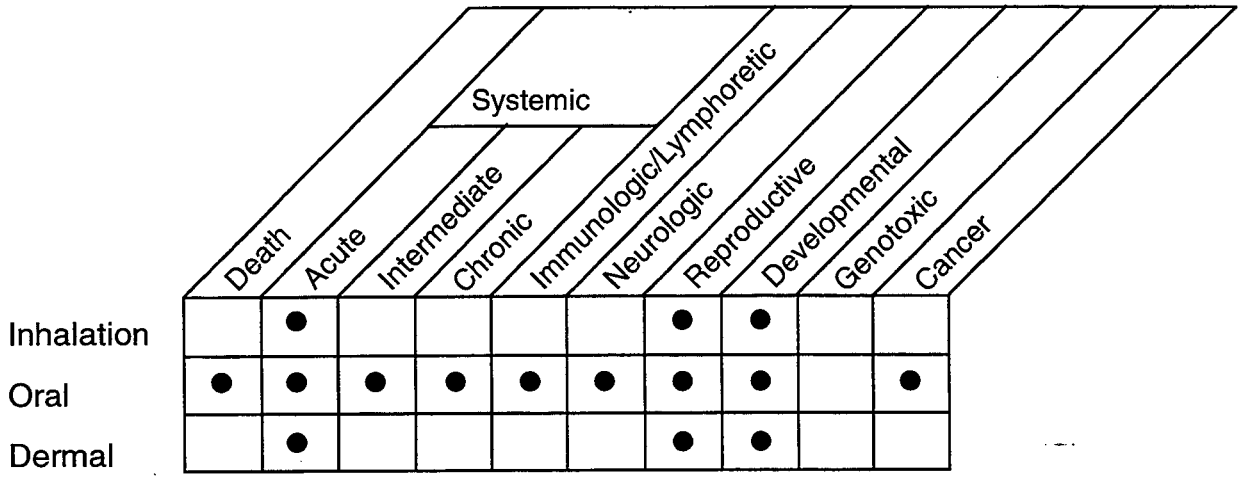
Existing information on health effects of ethylene glycol is shown in Figure 2-7, and existing information on the health effects of propylene glycol is shown in Figure 2-8. The purpose of these figures is to illustrate the existing information concerning the health effects of ethylene glycol and propylene glycol, respectively. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature..

The literature reviewed for health effects of ethylene glycol in humans came from one set of experimental data of acute-to-intermediate exposure of a group of 20 volunteers, one report of industrial exposure, and one epidemiological study of renal cancer mortality. Biological data, including hematology and blood chemistry, urinalysis, reports of respiratory irritation, and cancer

Figure 2-7. Existing Information on Health Effects of Ethylene Glycol



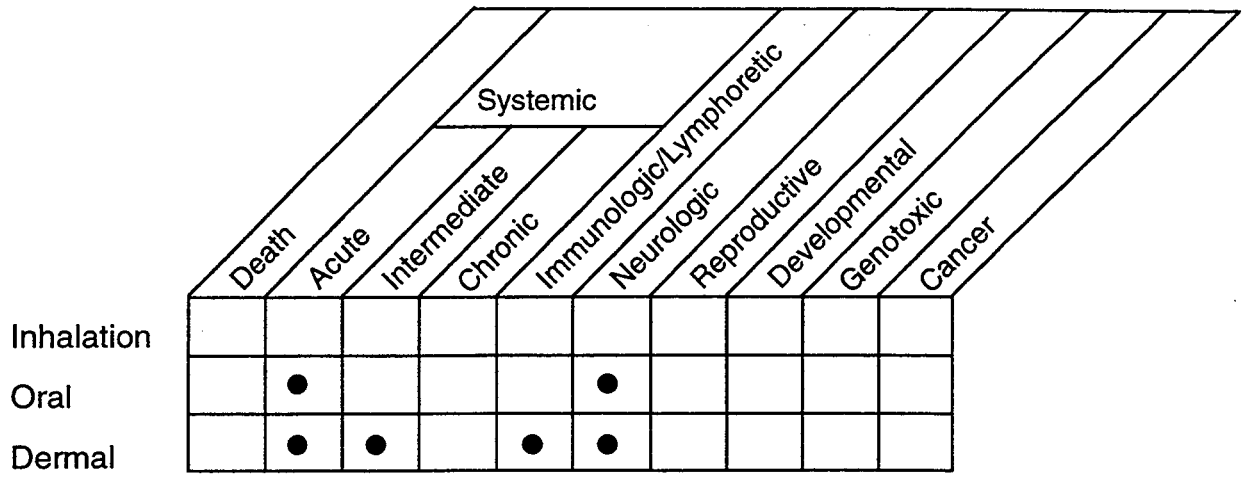
Human



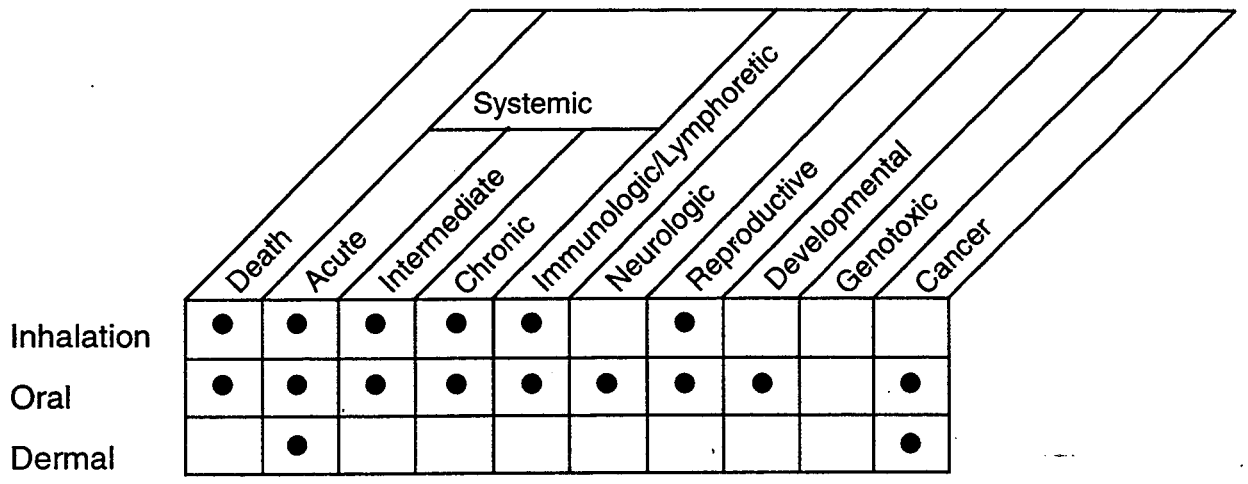
Animal

● Existing Studies

Figure 2-8. Existing Information on Health Effects of Propylene Glycol



Human



Animal

● Existing Studies

mortality were recorded. With the exception of the study of volunteers, no exposure levels could be determined from these reports. Therefore, the information on human inhalation exposure to ethylene glycol is limited. Data in animals for inhalation exposure is limited to two studies of developmental toxicity in rodents.

The database for the health effects of ethylene glycol following oral administration in humans and animals is more substantial. With respect to human exposure, case reports of accidental or intentional ingestion comprise the entire database. In these instances, exposure levels are not exact. Reports of oral exposure in animals are more complete and provide data for every health effect category, with the exception of *in vivo* measures of genotoxicity.

No reliable data describing health effects of ethylene glycol after dermal exposure in humans were found. A single report of occupational exposure was found, but the route of exposure and exposure level were not specified. Data describing health effects of ethylene glycol after dermal exposure in animals was contained in a single report of acute toxicity and one report of developmental toxicity.

People living near hazardous waste sites or near sites where ethylene glycol is manufactured or used in high volume (e.g., as a de-icing agent) may be exposed to ethylene glycol by ingestion of contaminated water, or by dermal contact with contaminated materials. In addition, inhalation or dermal exposure may occur in workers involved in high volume applications of ethylene glycol. Accidental or intentional ingestion of ethylene glycol remains a source of exposure, as does dermal exposure through handling of antifreeze solutions during automobile maintenance. Dermal exposure is the least likely route to cause toxicity, and can easily be prevented by using protective clothing. The health effects of oral exposure are fairly well documented, through accidental and intentional poisoning, and from animal studies. Therefore, inhalation exposure through high volume use remains the area likely to cause human health effects for which there is little data.

There is very little data on health effects of propylene glycol in humans. No data for humans were found for inhalation exposure of humans. Data exist for inhalation exposure of animals for acute-, intermediate-, and chronic-duration exposure.

Some acute oral data exist for humans, but the information is scanty and includes systemic, and neurological effects after acute exposure. Propylene glycol is considered GRAS by the FDA, and thus

oral exposure through foods is considered safe. With respect to this, animal data for oral exposure are more extensive, and all categories of health effects except in vivo genotoxicity are included.

Propylene glycol is used extensively in topical drug formulations and cosmetics. The majority of reports of human dermal studies describe sensitivity reaction (or, lack of reaction) to these preparations. Human dermal data includes acute-duration effects, and immunological and neurological effects. Animal data describing dermal exposure are limited to acute-duration effects and an evaluation of immunological and neurological effects.

People living near hazardous waste sites or near sites where propylene glycol is manufactured may be exposed to propylene glycol by ingestion of contaminated water. Since propylene glycol is an approved food additive, ingestion of small amounts would not be considered a health risk. Inhalation exposure is not a likely route for toxic health effects. Dermal exposure to propylene glycol has been associated with sensitivity reactions, although the data are confusing. Increased use of propylene glycol in foods and cosmetics, and as a substitute for ethylene glycol suggests that general exposure to propylene glycol will be more frequent and at higher levels than previously experienced by the general population. Therefore, additional research in these areas may be warranted.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. Little information is available regarding the effects of acute-duration respiratory exposure to ethylene glycol in humans. Only one study exists in the literature, describing health effects of 20 volunteers after acute-duration inhalation exposure (Wills et al. 1974). Respiratory irritation was observed during the acute-duration exposure, but no other effects were reported. Two reports were found describing acute-duration inhalation exposure of rats and mice (Tyl 1985, 1988a). More reports of acute-duration oral exposure were found for humans (Berger and Ayyar 1991; Blakely et al. 1993; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Gordon and Hunter 1982; Heckerling 1987; Hewlett et al. 1986; Jacobsen et al. 1984, .1988; Karlson-Stiber and Pen-son 1992; Mallya et al. 1986; Oliver0 1993; Parry and Wallach 1974; Peterson et al. 1981; Rothman et al. 1986; Siew et al. 1975a; Spillane et al. 1991; Underwood and Bennett 1973; Walton 1978; Woolf et al. 1992; Zeiss et al. 1989) and animals (Adams et al. 1991; Beckett and Shields 1971; Clark et al. 1979; Clay and Murphy 1977; Dial et al. 1989; Ebisuno et al. 1987; Grauer et al. 1987; Harris et al 1992; Hong et al. 1988; Kersting and Nielsen 1965; Man- et al. 1992; Neeper-

Bradley 1990; NTP 1988; Penumarthy and Oehme 1975; Price et al. 1985; Richardson 1973; Roberts and Seibold 1969; Schuler et al. 1984; Tyl 1989; Tyl et al. 1993). No studies of acute-duration dermal exposure to ethylene glycol in humans were found, although two studies in animals were located (Clark et al. 1979; Tyl 1988b).

Death can occur in humans after ingestion of ethylene glycol (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsin et al. 1984; Siew et al. 1975a; Zeiss et al. 1989), and also in animals (Adams et al. 1991; Beckett and Shields 1971; Clark et al. 1979; Kersting and Nielson 1965; Penumarthy and Oehme 1975; Richardson 1973; Schuler et al. 1984; Tyl et al. 1993). The main targets of ethylene glycol toxicity following acute exposure are the kidney and the developing fetus (Adams et al. 1991; Beckett and Shields 1971; Berger and Ayyar 1981; Blakely et al. 1993; Chung and Tuso 1989; Ebisuno et al. 1987; Factor and Lava 1987; Godolphin et al. 1980; Gordon and Hunter 1982; Heckerling 1987; NTP 1988; Price et al. 1985; Roberts and Seibold 1969; Schuler et al. 1984; Tyl 1989; Tyl et al. 1988a).

An acute-duration MRL was derived for inhalation exposure to ethylene glycol based on increased kidney weight in mice (Tyl et al. 1988a). An acute-duration MRL was derived for oral exposure, based on developmental toxicity in mice (Tyl 1989). Additional acute-duration dermal studies may be helpful in evaluating this route of exposure.

No information was available for acute-duration inhalation exposure to propylene glycol in humans. Only one study in animals was found to provide some information for acute-duration inhalation exposure (Konradova et al. 1978). Rabbits were exposed to only one dose (10% aerosol) of propylene glycol for 20 or 120 minutes, and an increased number of degenerated goblet cells in the tracheal lining was observed. No other data were available from this study and the importance of these findings is unclear. Information regarding acute-duration oral exposure to propylene glycol in humans (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987) and animals is more abundant (Clark et al. 1979; Dorman and Haschek 1991; Kavlock et al:1987; Morshed et al. 1991a; Ruddick 1972; Studer et al. 1993; Weiss et al. 1992). Acute-duration dermal exposure to propylene glycol in humans (Commens 1990; Corazza et al. 1993; Eun and Kim 1989; Fligner et al. 1985; Kinnunen and Hannuksela 1989; Kulick et al. 1985; Willis et al. 1988) and animals has been reported (Clark et al. 1979), although data are scarce.

Death has been shown to occur after acute-duration oral exposure to propylene glycol (Clark et al. 1979; Dorman and Haschek 1991; Gordon and Hunter 1982; Ruddick 1972). With the exception of hematological effects in cats after oral exposure (Weiss et al. 1992), there does not appear to be a target system for propylene glycol effects. Sensitization reactions have been reported in humans after acute-duration dermal exposure (Corazza et al. 1993; Hannuksella and Forstrom 1978).

No acute-duration inhalation MRL could be derived for propylene glycol because no adequate studies were found. In the single acute-duration inhalation study found in the literature (Konradova et al. 1978), only one dose was used, and sufficient information was not provided on which to base and MRL. No acute-duration oral MRL could be derived for propylene glycol because no adequate studies were found. With regard to the human studies (Frosch et al. 1990; Hannuksella and Forstrom 1978; Lolin et al. 1988; Nelson et al. 1987), only one dose was tested, data were sparse, or the exact dose was not known. Acute-duration oral studies in animals focused on death (Clark et al. 1979; Ruddick 1972), involved a single dose (Dorman and Haschek 1991; Kavlock et al 1987; Morshed et al. 1991a; Studer et al. 1993), or discussed species-specific effects (Weiss et al. 1992). Thus, none of these studies were adequate for deriving an MRL.

Intermediate-Duration Exposure. Only one study describing intermediate-duration inhalation exposure of humans to ethylene glycol was found (Wills et al. 1974), and no studies were found for animals. Oral intermediate-duration exposure data for ethylene glycol was not found for humans, but is more abundant for animals (DePass et al. 1986b; Harris et al. 1992; Khan et al. 1993; Lamb et al. 1985; Melnick 1984; Nagano et al. 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986). No data were found for intermediate-duration dermal exposure to ethylene glycol in either humans or animals.

Death has been reported after intermediate-duration oral exposure to ethylene glycol in rats (Melnick et al. 1984). As in the acute-duration studies, renal (DePass et al. 1986b; Khan et al. 1993; Melnick 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986) and reproductive and deiielopmental toxicity (Harris et al. 1992; Lamb et al. 1985) were observed in animals after intermediate-duration exposure.

No intermediate-duration inhalation or oral MRLs could be derived for ethylene glycol because no appropriate studies were found. With regard to inhalation exposure, the intermediate-duration portion

of the study (Wills et al. 1974) did not provide an adverse effect level for less serious effects that could be attributed to ethylene glycol. For oral exposure, all appropriate and adequate studies found (DePass et al. 1986b; Harris et al. 1992; Khan et al. 1993; Lamb et al. 1985; Melnick 1984; NTP 1992; Roberts and Seibold 1969; Rofe et al. 1986) had NOAELs and LOAELs that were higher than the NOAEL and LOAEL in the study chosen for the acute-duration oral MRL (Tyl et al. 1988a).

No studies of intermediate-duration inhalation exposure of humans to propylene glycol were found. One intermediate-duration inhalation study of propylene glycol in rats was found in the literature (Suber et al. 1989). No studies of intermediate-duration oral exposure of humans to propylene glycol were found. Studies of intermediate-duration oral exposure of animals were more abundant (Bauer et al. 1991; Christopher et al. 1989a; Morshed et al. 1991a; NTP 1985; Weiss et al. 1990). No studies of intermediate-duration dermal exposure to propylene glycol were found in animals. One intermediateduration dermal exposure study in humans described primarily dermal irritative effects of propylene glycol (Trancik and Maibach 1982).

No reports of death in animals after intermediate-duration exposure to propylene glycol were found. Systemic effects after inhalation exposure of rats included nasal hemorrhaging, hematological effects, and decreased kidney and body weight (Suber et al. 1989). Cats exhibit characteristic hematotoxicity (Heinz body formation) after intermediate-duration oral exposure (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), although no other targets for toxicity were apparent.

An intermediate-duration inhalation MRL was derived for propylene glycol based on nasal hemorrhaging in rats (Suber et al. 1989). No intermediate-duration oral MRL could be derived due to a lack of suitable studies. Of the intermediate-duration oral exposure studies found, none were in humans; animal studies included species-specific effects in cats (Bauer et al. 1991; Christopher et al. 1989a; Weiss et al. 1990), studies with a single dose (Morshed et al. 1991a), or studies with no adverse effects observed (NTP 1985).

Chronic-Duration Exposure and Cancer. Few studies were found describing chronic-duration inhalation exposure to ethylene glycol in humans, and no studies were found describing chronicduration inhalation exposure to ethylene glycol in animals. One report of an industrial exposure by inhalation over a period of 2 years described hematological and neurological effects, but an exposure level could not be determined (Triosi 1950). In the other study describing chronic occupational

exposure, the renal cancer mortality rate of a cohort of former employees of a chemical plant was determined (Bond et al. 1985); exposure level was not determined in this study either. Thus, human data for chronic inhalation exposure is scanty.

No studies of chronic-duration oral exposure to ethylene glycol in humans were found. Several chronic-duration oral exposure animal studies were found (Blood 1962, 1965; DePass et al. 1984, 1986a; Morris et al. 1942; NTP 1992; Woodside 1982).

Only one study was found that could be classified as chronic-duration dermal exposure to ethylene glycol (Bond et al. 1985). In this epidemiological study of renal cancer mortality, dermal exposure in the occupational setting is assumed. Exposure levels were not determined. No chronic-duration dermal studies of ethylene glycol in animals were found.

Death was observed in rats after chronic-duration oral exposure to ethylene glycol in the feed (Blood 1965; DePass et al. 1986a; Morris et al. 1942; Woodside 1982). Death rates were 70-100% after exposure to doses of 500 mgkglday or greater for more than 12 months. Males were more sensitive than females. Death was not observed in humans after chronic-duration inhalation or dermal exposure (Bond et al. 1985; Triosi 1950). After chronic-duration inhalation exposure of women working in a factory, increased lymphocyte count was found (Triosi 1950). In the other study describing chronic occupational exposure, the renal cancer mortality rate of a cohort of former employees of a chemical plant was determined and found not to be correlated with inhalation exposure to ethylene glycol (Bond et al. 1985).

Data describing systemic effects from chronic-duration oral exposure in animals is more abundant. No adverse effects on the histopathology of tissues, including kidneys, were observed in rhesus monkeys exposure to 200 mg/kg day ethylene glycol in the feed for 3 years (Blood et al. 1962). Male rats exposed to 500 mg/kg/day ethylene glycol in the feed for 2 years exhibited oxalate crystals and proteinuria prior to death, whereas female rats exposed to ethylene glycol in the same study exhibited these renal effects at 2,000 mg/kg/day (Blood 1965). The sensitivity of the male rat to the renal effects of ethylene glycol were also observed by DePass et al. (1986a), and Woodside (1982). Male Fischer rats exhibited oxalate nephrosis and chronic nephritis after exposure to 1,000 mg/kg/day ethylene glycol in the feed for 12 months, whereas females only exhibited elevated urinary oxalate at the same dose. Adverse renal effects, including kidney stones, tubular atrophy, and tubular casts were

also noted by Morris et al. (1942) after chronic oral exposure to ethylene glycol. Other effects noted in rats included decreased hematocrit, reduced REK, reduced hemoglobin, and increased neutrophils in males (DePass et al. 1986a; Woodside 1982), fatty metamorphosis of the liver in females (Depass et al. 1986a; Woodside 1982), and hepatic atrophy and bile duct proliferation (Morris et al. 1942). Mice appear to be less sensitive to the toxic effects of orally administered chronic-duration ethylene glycol. No adverse effect on liver, kidney, or other organ systems was observed in CD-1 mice exposed to 1,000 mg/kg/day ethylene glycol in the feed for 2 years (DePass et al. 1984). Only after exposure to doses of 1,625 mg/kg/day or greater for 2 years were adverse effects, including pulmonary arterial medial hyperplasia, hyaline degeneration of the centrilobular hepatocytes, and oxalate nephrosis observed in mice (NTP 1992). In this study, also, males were more sensitive than females (NTP 1992). No evidence of increased tumorigenesis was observed in the oral chronic-duration rodent studies (DePass et al. 1984, 1986a; NTP 1992; Woodside 1982).

No chronic-duration inhalation MRL could be derived due to a lack of appropriate studies. A chronicduration oral MRL was derived based on renal toxicity in male rats after chronic exposure to ethylene glycol in the feed (DePass et al. 1986a; Woodside 1992). .

No chronic-duration studies of human exposure to propylene glycol alone by inhalation, oral, or dermal administration were found in the literature. One study of chronic-duration inhalation exposure of animals (Robertson et al. 1947), and one study of dermal exposure of animals (Stenback and Shubik 1974) were found. Data for chronic-duration oral exposure of animals to propylene glycol is more abundant (Gaunt et al. 1972; Morris et al. 1942; Weil et al. 1971). Tumorigenesis was evaluated after inhalation and dermal exposure (Robertson et al. 1947; Stenback and Shubik 1974).

After inhalation exposure to propylene glycol for 13 months, 13 of 29 rhesus monkeys died (Robertson et al. 1947). Death was not observed in rats or dogs after exposure to oral doses of propylene glycol of 2,500 or 5,000 mg/kg/day, respectively, for 2 years (Gaunt et al. 1972; Weil et al. 1971). No reports of death after dermal exposure were found. Systemic effects noted after inhalation. exposure of animals to propylene glycol were few, and included increased hemoglobin in monkeys and increased body weight in rats (Robertson et al. 1947). Similarly, only hematological effects, including decreased erythrocytes, hemoglobin, and hematocrit were observed in dogs at 5,000 mg/kg/day (Weil et al. 1971).

No evidence of tumorigenesis was noted after oral exposure of rats to doses of propylene glycol up to 2,500 mg/kg/day for 2 years (Gaunt et al. 1972), or dermal exposure of mice to 20 mg applied twice weekly for 120 weeks (Stenback and Shubik 1974).

No MRLs for chronic-duration inhalation exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. No studies were found for humans, and in the one animal study found (Robertson et al. 1947), the effects cited (increased hemoglobin and body weight) were not appropriate effects on which to base an MRL. No MRLs for chronic-duration oral exposure to propylene glycol could be derived due to a lack of appropriate studies in the literature. In the one study found (Gaunt et al. 1972), no adverse effects were noted.

Immunological and Lymphoreticular Effects. Ethylene glycol does not seem to have any characteristic adverse immunological effects. There were no studies that specifically addressed immunological effects in humans or animals. Data in the literature are sparse and conflicting (DePass et al. 1986a; Spillane et al. 1991; Underwood and Bennett 1973; Wills et al. 1974; Woodside 1982). Further evaluation of the immunological and lymphoreticular effects of ethylene glycol would be useful in assessing the effects of ethylene glycol exposure by inhalation, oral, and dermal routes.

Since propylene glycol is used in topical formulations, it has been investigated as both an irritant and contact allergen (Hannuksela et al. 1975; Kinnunen and Hannuksela 1989; Tranick and Maibach 1982; Willis et al. 1988). Results indicate that except in rare cases (Corrazza et al. 1993; Hannuksela et al. 1975; Trancik and Maibach 1982) the irritative properties of propylene glycol are minimal (Aberer et al. 1993; Hannuksela and Forstrom 1978; Willis et al. 1989). There was no effect on the spleen in rats or monkeys exposed to 112 ppm aerosolized propylene glycol for up to 18 months (Robertson et al. 1947; Suber et al. 1989).

Propylene glycol in a concentration of 0.5-1.0% has been shown to inhibit natural cytotoxicity and neutrophil chemiluminescence in human cells *in vitro* (Denning and Webster 1987). The authors suggest that propylene glycol has cytotoxic properties and should be evaluated in light of this information.

The data describing the immunotoxicity of propylene glycol is not clear. Further *in vivo* animal studies would be helpful in defining the immunotoxic effects of propylene glycol.

Neurological Effects. Few data are available describing neurological effects of dermal or inhalation ethylene glycol exposure. The data that are available indicate that acute oral intoxication is the source of the most characteristic neurological manifestations. Specifically, adverse neurological reactions are among the first symptoms to appear in human ethylene glycol poisoning. These are the only symptoms that are attributable directly to ethylene glycol, and resemble ethanol intoxication. They occur within 30 minutes to 12 hours after exposure, and include ataxia, disorientation, restlessness, slurred speech, and somnolence, progressing to convulsions and coma (Cheng et al. 1987; Factor and Lava 1987; Gordon and Hunter 1982; Robinson and McCoy 1989; Vale 1979; Woolf et al. 1992). These symptoms may be ameliorated by supportive therapy. Some evidence exists that damage to the cranial nerves may occur much later in the toxic process, especially if supportive therapy is delayed (Chung and Tuso 1989; Factor and Lava 1987; Mallya et al. 1986; Spillane et al. 1991). Similar effects have been seen in laboratory animals after large oral doses of ethylene glycol were administered (Beckett and Shields 1971; Clark et al. 1979; Penumarthy and Oehme 1975). In vitro studies of the effect of ethylene glycol on nerve cell cultures from Wistar rats indicate that ethylene glycol caused neuronal degeneration, decreased in acetylcholinesterase-containing cells, and reactive cellular grouping (Capo et al. 1993). The neurological effects of ethylene glycol after oral exposure appear to be fairly well defined. Further studies of this route of exposure are not warranted. However, little or no data are available describing neurological effects after inhalation or dermal exposure to ethylene glycol. Additional data for these routes of exposure would be helpful in comparing the potential for neurological effects after inhalation or dermal exposure with the welldefined effects observed after oral exposure.

Mild neurological effects have been observed in dermally sensitive individuals after an oral challenge dose of 2-15 mL of propylene glycol (Hannuksela and Forstrom 1978). In the case of ingestion of a large amount of propylene glycol, neurotoxic symptoms including stupor and repetitive convulsions were noted (Lolin et al. 1988). Neurological effects were also noted in patients receiving 887 mg/kg propylene glycol 3 times daily, but those effects were complicated by co-ingestion of ethanol (Yu et al. 1985). Adverse effects have also been observed in rats prior to death (Clark et al. 1979) and in cats (Christopher et al. 1990b). Based on these data, however, it seems unlikely that low level exposure to propylene glycol would cause neurotoxicity. Further studies of the neurological effects of propylene glycol would be helpful in defining the toxicity of the compound.

Reproductive Toxicity. Studies have not addressed the reproductive toxicity of ethylene glycol in humans. Mice showed some degeneration of the seminiferous tubules after oral exposure (Hong et al. 1988). In addition, female mice orally exposed to ethylene glycol for 20 days, and mated on the eighth day of exposure with males that had been treated for 17 days prior to mating, had fewer live litters, more dead implants, and more litters totally resorbed (Harris et al. 1992). However, male mice showed no direct effects on the reproductive system, suggesting that the effects originated with the female (Harris et al. 1992). In a multi-generation continuous breeding study done in CD-l mice (Lamb et al. 1985), intermediate exposure to 1% ethylene glycol in drinking water slightly decreased the fertility of the exposed parental and F_1 generations. Most other studies indicate no direct adverse effects of ethylene glycol on the reproductive organs (Depass et al. 1986a; Nagano et al. 1984). Ethylene glycol does not appear to cause direct effects on the reproductive tissues, and further studies are not warranted.

Studies in humans have not addressed whether propylene glycol adversely affects the reproductive system. In rats and mice, no adverse effects on the reproductive competence of these animals were observed after oral treatment at doses as high as 10,000 mgkglday during gestation of 1 generation or for multiple litters and 2 generations of mice (Kavlock et al. 1987; NTP 198.5) or inhalation exposure to 112 ppm for 18 months (Robertson et al. 1947). Further evaluation of the reproductive toxicity of propylene glycol is not necessary.

Developmental Toxicity. Studies have not addressed the developmental toxicity of ethylene glycol in humans. Female mice and rats exhibit adverse effects on developmental parameters after exposure to ethylene glycol during gestation at doses of 2,100-2,500 ppm or 400 ppm, respectively, by nose-only inhalation (Tyl 1988a), and 500 or 750 mg/kg/day by gavage (Price et al. 1985; Tyl 1989). Rabbits receiving 2,000 mg/kg/day ethylene glycol by gavage showed no adverse developmental effects (Tyl et al. 1993). No effects were seen after dermal exposure of mice to doses up to 3,549 mg/kg (Tyl 1988b). Thus, inhalation or oral exposure during organogenesis to relatively large doses of ethylene glycol may adversely affect the developmental process. However, ev”ldence exists in laboratory studies that these adverse effects can be eliminated by correcting the metabolic acidosis that accompanies ethylene glycol exposure (Khera 1991) (see Section 2.7). Thus, the developmental effects of ethylene glycol poisoning may be preventable with proper supportive therapy.

In vitro studies of rat embryo development indicate that ethylene glycol is embryotoxic (Grafton and Hansen 1987). Ethylene glycol added to culture medium decreased the morphological score, somite number, crown-rump length, and head length, as well as DNA and protein content of rat embryos. Absence of yolk sac circulation, absent hindlimb bud, hypoplastic telencephalon, and lack of development of the otic and optic systems were also seen in exposed embryos. The developmental toxicity of ethylene glycol is fairly well defined. Further evaluation of the developmental toxicity of ethylene glycol toxicity is not warranted.

Propylene glycol does not appear to be a developmental toxicant in animals. Pregnant female Swiss mice given 10,000 mg/kg/day propylene glycol by mouth on Gd 8-12 showed no adverse developmental effects (Kavlock et al. 1987). No adverse effects of propylene glycol on the development of Swiss (CD-l) mice were noted after doses of approximately 10,000 mg/kg/day (NTP 1985). *In vitro* studies of embryonic development suggest that propylene glycol alters the development of mouse zygotes (Damien et al. 1989, 1990). Treatment with propylene glycol caused cell membrane damage and altered pH, resulting in a decrease in embryonic development. The relevance of these results to *in vivo* exposure is not clear. Further studies of developmental toxicity of propylene glycol do not appear to be necessary.

Genotoxicity. Although neither ethylene glycol or propylene glycol has been extensively evaluated in genetic toxicity test systems, the existing studies provide convincing evidence that neither compound is genotoxic. Ethylene glycol was negative for dominant lethal mutations in rats (DePass et al. 1986b), S. *typhimurium* assays gave uniformly negative results (Clark et al. 1979; McCann et al. 1975; Pfeiffer and Dunkelberg 1980; Zeiger et al. 1987), and no growth inhibition due to DNA damage by ethylene glycol was observed in a battery of *E. coli* repair-deficient strains (McCarroll et al. 1981). Negative results were also obtained in two sets of studies when ethylene glycol was tested for gene mutation in the yeast *S. pombe* (Abbondandolo et al. 1980), and for aneuploidy induction in the fungus N. C~USSU (Griffiths 1979, 1981). Because of the information available in *in vitro* culture and animals, it is reasonable to conclude that exposure to ethylene glycol poses minimar risk of causing genotoxic effects in exposed persons, and that no further studies are necessary.

Studies in humans or animals have not addressed whether adverse genotoxic effects occur after *in vivo* exposure to propylene glycol. However, propylene glycol was not mutagenic in *S. typhimurium* strains with and without metabolic activation (Clark et al. 1979; Pfeiffer and Dunkelberg 1980). In addition,

propylene glycol was negative for sister chromatid exchange and changes in alkaline elution rate using Chinese hamster cells or human fibroblasts (Sasaki et al. 1980 as cited in Abe et al. 1982; Swenberg et al. 1976). Based on these results, it seems likely that propylene glycol does not represent a genotoxic risk to exposed persons. An in *vivo* study would complete the database of the genotoxic effects of propylene glycol.

Epidemiological and Human Dosimetry Studies. No reliable epidemiological studies of ethylene glycol exposure are available. Individuals who work with ethylene glycol in high volume applications, such as de-icing aircraft and routine automobile maintenance, are the populations most likely to be at risk for toxic effects. Epidemiological and human dosimetry studies.after inhalation and dermal exposure would be helpful in further evaluating ethylene glycol toxicity in these subpopulations.

No reliable epidemiological studies of propylene glycol exposure are available. Increased use of propylene glycol in food and in drugs and cosmetics suggests that oral and dermal exposure are the most important routes of exposure for the general population. In addition, the substitution of propylene glycol in applications where ethylene glycol was previously used will create new subpopulations for exposure. Bpidemiological and human dosimetry studies of these subpopulations would be helpful in evaluating propylene glycol toxicity in these increased applications of use.

Biomarkers of Exposure and Effect.

Exposure. Exposure to ethylene glycol can be measured by determining the levels of ethylene glycol in the blood. Presence of ethylene glycol in the blood would indicate a very recent exposure. Since ethylene glycol blood levels show no direct correlation to the degree of toxicity, blood levels are only of value in establishing exposure. Ethylene glycol concentrations in urine are higher than ethylene glycol concentrations in serum; thus, it remain detectable for a longer period. Rapid methods for determining ethylene glycol in serum and urine are available for use in the clinical setting (Aarstad et al. 1993; Blandford and Desjardins 1994).

Because ethylene glycol is rapidly absorbed and biotransformed in the body, some of its metabolic products may be used to identify exposure to ethylene glycol. Metabolic acidosis due to increased amounts of glycolic acid and lactic acid occurs in cases of intoxication with ethylene glycol (Jacobsen

et al. 1984). However, lactic acid is not a specific marker for ethylene glycol exposure; thus, it has no use as a biomarker in this instance. In cases of exposure to ethylene glycol, there is a small increase in the amount of oxalic acid in blood, contributing to metabolic acidosis. As oxalic acid interacts with calcium from the body, it forms calcium oxalate crystals which can be detected in the urine (Jacobsen et al. 1988). Glycolic acid can be used as a relatively sensitive indicator of ethylene glycol exposure due to its relatively high production from ethylene glycol and its rapid clearance from the body. Rapid and accurate methods of analysis now exist for glycolic acid in serum (Fraser and MacNeil 1993). Calcium oxalate is a less sensitive marker due to its slow formation and its relatively slow clearance from the body. Both serum glycolic acid and urinary calcium oxalate have been used to identify exposure to ethylene glycol. Further studies of biomarkers of exposure to ethylene glycol are not a data need.

Propylene glycol can also be detected in the blood a short time after exposure to a large amount. There are no other specific biomarkers for propylene glycol exposure. Since propylene glycol is considered a safe additive for food, cosmetics, and pharmaceuticals, other specific tests of propylene glycol exposure have not been developed. Further evaluation of possible biomarkers of exposure to propylene glycol would be helpful, especially in light of increased use of propylene glycol in food, cosmetics, and drugs.

Effect. Adverse neurological reactions that can culrnmate in convulsions and coma are among the first symptoms in humans after ethylene glycol intoxication (Zeiss et al. 1989). Some of the most common manifestations of ethylene glycol neurotoxicity include ataxia, slurred speech, semiconsciousness, unresponsiveness, and somnolence (Anonymous 1987; Cheng et al. 1987; Chung and Tuso 1989; Factor and Lava 1987; Parry and Wallach 1974; Rothman et al. 1986; Spillane et al. 1991; Underwood and Bennett 1973). Several more recent studies described adverse effects of ethylene glycol on cranial nerves; the symptoms appear later and may involve facial paralysis, bilateral optic nerve dysfunction, and peripheral neurosensory hearing loss. These symptoms are not specific to ethylene glycol, but in conjunction with known or suspected exposure, may serve to guide diagnosis and treatment.

The presence of calcium oxalate monohydrate crystals is the hallmark of ethylene glycol intoxication. The crystals can be deposited in renal tubules and/or excreted in urine after exposure to relatively large amounts of ethylene glycol (Anonymous 1987; Chung and Tuso 1989; Factor and Lava 1987; Godolphin et al. 1980; Heckerling 1987; Parry and Wallach 1974; Rothman et al. 1986; Siew et al.

1975a; Underwood and Bennett 1973). In some cases, there is only a brief period of calcium oxalate dihydrate crystalluria (Jacobsen et al. 1988). Renal toxicity can also be indicated by increased serum levels of BUN or creatinine; however, this occurs relatively late in intoxication (i.e., stage 3, 48-72 hours post ethylene ingestion) and is not specific for ethylene glycol intoxication (Grauer et al. 1987).

Respiratory system involvement occurs 12-24 hours after ingestion of ethylene glycol. The symptoms include hyperventilation (Godolphin et al. 1980), shallow rapid breathing (Zeiss et al. 1989), and generalized pulmonary edema (Vale 1979).

Cardiovascular system involvement occurs during the second phase of ethylene glycol poisoning, at the same time as the respiratory system involvement. The symptoms are tachycardia, ventricular gallop, and ventricular dilation (Parry and Wallach 1974; Siew et al. 1975a; Vale 1979). As in the case of respiratory effects, cardiovascular involvement occurs after exposure to relatively high oral levels of ethylene glycol. Both of these types of effects are not specific to ethylene glycol intoxication. Further evaluation of biomarkers of ethylene glycol effects is not a data need.

Propylene glycol is not associated with any specific biomarkers of effect. Dermal irritation may occur after repeated exposure, and suspect drug or cosmetic preparations should be examined closely for propylene glycol content. In light of the increased use of propylene glycol in foods, cosmetics, and drugs, identification of biomarkers of propylene glycol effect would be useful in evaluating biological effects of propylene glycol exposure.

Absorption, Distribution, Metabolism, and Excretion. No kinetic data for absorption, distribution, metabolism, or excretion in humans or animals of ethylene glycol after inhalation exposure were found in the literature. Since human exposure to ethylene glycol is usually oral by accidental means, or intentional ingestion (Godolphin et al. 1980; Gordon and Hunter 1982; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Karlson-Stilber and Persson 1992; Litovitz et al. 1990, 1991; Peterson et al. 1981; Siew et al. 1975a; Walton 1978; Zeiss et al. 1989) or dermal contact, without records of the amount ingested, few data describing the complete kinetics of ethylene glycol after human oral exposure were found in the literature, and no data describing the kinetics of *in vivo* human dermal exposure were found in the literature.

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There are several human studies (Cheng et al. 1987; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Peterson et al. 1981; Rothman et al. 1986), and a number of animal studies describing absorption, distribution, metabolism, and excretion of ethylene glycol after in viva oral or dermal exposure (Dial et al. 1989, 1994; Frantz et al. 1989, 1991; Hewlett at al. 1989; Martis et al. 1982; Rofe et al. 1986; Winek et al. 1978). Information is available to assess the relative rates and extent of these parameters by the oral route in humans and animals and, to a lesser extent, by the dermal route in humans *in vitro* and in animals *in vivo* and *in , vitro.* All of the toxicokinetic data involve acute exposures to ethylene glycol. No data deal with intermediate- or chronic-duration exposures. Intermediate- and chronicduration data are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for these durations. No data were located regarding the absorption, distribution, and excretion of ethylene glycol after inhalation exposure. Acute-, intermediate-, and chronic-duration exposure data are needed to adequately assess the relative rates and extent of the toxicokinetic parameters by this route. No data were located for the toxicokinetic parameters of ethylene glycol exposure in humans after dermal contact. In light of the uses of ethylene glycol, data regarding *in vivo* human exposure would be helpful in evaluating relative risk of exposure by this route.

No kinetic data for absorption, distribution, metabolism, or excretion in humans or animals of propylene glycol after inhalation exposure were found in the literature. Few data were found in the literature describing the kinetics of propylene glycol in humans after oral exposure (Yu et al. 1985), but more data were found for animals (Christopher et al. 1990b; Huff 1961; Miller and Bazzano 1965; Morshed et al. 1988, 1989, 1991a). Since propylene glycol is used in topical drug preparations, limited data are available for kinetic parameters in humans after dermal exposure (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990), and in animals (Rigg and Barry 1990; Takeuchi et al. 1993, 1995). Most of these data concern acute exposures and are limited because propylene glycol is considered a safe and innocuous compound. No data were located regarding kinetic parameters of propylene glycol after inhalation exposure. Studies are needed in order to adequately assess the rates and extent of the toxicokinetic parameters for this route. In light of increased use of propylene glycol as a food additive, and in cosmetics and topically applied drugs, additional studies of the absorption, distribution, metabolism, and excretion of propylene glycol after oral and dermal exposure for acute-, intermediate-, and chronic-duration exposure would be helpful in assessing the kinetic properties of the compound by these routes.

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Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of ethylene glycol have been studied in animals (Dial et al. 1989, 1994; Frantz et al. 1989, 1991; Hewlett at al. 1989; Martis et al. 1982; Rofe et al. 1986; Winek et al. 1978), and to a lesser extent in humans (Cheng et al. 1987; Hewlett et al. 1986; Jacobsen et al. 1984, 1988; Peterson et al. 1981; Rothman et al. 1986). The target organs identified in humans include the kidney and neurological system. The target organs identified in animals included the kidney and developing fetus. Ethylene glycol causes metabolic acidosis in both humans and animals. Based on data in both humans and animals, ethylene glycol toxicity is the result of metabolic acidosis and calcium oxalate production. Prevention of these toxic effects can be accomplished by interfering with the metabolism of ethylene glycol. Most of the toxicokinetic studies, have been conducted using rats, since mice appear to be less sensitive and less like humans with regard to toxic sequelae after ethylene glycol exposure. Based on the available data, humans would be expected to handle ethylene glycol in a manner similar to rats, although data indicate that predictions based on rodent data tend to overestimate human response.

The kinetics of propylene glycol have been studied in animals (Morshed et al. 1988; Rigg and Barry 1990; Takeuchi et al. 1993, 1995) and to a lesser extent in humans (Fligner et al. 1985; Kulick et al. 1985; Rigg and Barry 1990; Yu et al. 1985). However, information on the toxicokinetic properties of propylene glycol are limited, based on its nontoxic status. No specific target organs have been identified for propylene glycol, although neurological effects have been noted after oral exposure (Clark et al. 1979; Hannuksela and Forstom 1978; Lolin et al. 1988; Yu et al. 1985). Propylene glycol also causes metabolic acidosis, although to a lesser extent than ethylene glycol (Lolin et al. 1988; Morshed et al. 1989, 1991b). Little data exist to assist in interspecies comparison of kinetic parameters. In light of increased use of propylene glycol in foods, cosmetics, and drugs, and as a substitute for ethylene glycol, additional inhalation, oral, and dermal kinetic studies would be helpful in predicting human kinetic response to propylene glycol exposure.

Methods for Reducing Toxic Effects. Clinical methods for reducing ethylene glycol absorption after oral exposure include gastric lavage, charcoal slurry, or emesis. However, no studies on reducing peak absorption following inhalation or dermal exposure were found. Cleaning the skin after dermal exposure would be essential in reducing absorption.

Metabolic acidosis is a common symptom of ethylene glycol toxicity. The primary therapies are aimed at this toxic effect. Clinical case histories from accidental and intentional ingestion of ethylene

glycol show that metabolic acidosis can be controlled and eliminated. Administration of bicarbonate to correct the blood pH, and ethanol to compete for the enzymes that convert ethylene glycol to glycolic acid, can prevent any sequelae of ethylene glycol poisoning if administered early enough. Fluid therapy and volume expansion, and diuresis are also important treatments for ethylene glycol poisoning. Peritoneal and hemodialysis are useful therapies for reducing the toxic effects of ethylene glycol. In laboratory studies, Khera (1991) has shown that in rats, correction with bicarbonate of metabolic acidosis caused by ethylene glycol administration reduced or prevented subsequent developmental anomalies. Thus, proven methods of reducing the toxic effects of ethylene glycol exist and can be used in the event of a toxic exposure. Rofe et al. (1986) found that coadministration of a diet supplemented with sucrose increased renal calcium oxalate deposition in rats. This study suggests that administering a diet low in carbohydrates may be helpful in reducing calcium oxalate deposition in the kidneys after ethylene glycol exposure.

Magnesium and vitamin B6 have been found to reduce the toxicity of ethylene glycol in animals (Browning 1965; Gershoff and Andrus 1962; Khan et al. 1993), whereas a deficiency of these essential nutrients accelerates toxicity (Ebisuno et al. 1987; Gershoff and Andrus 1962). Thus, administration of magnesium may aid in preventing calcium oxalate deposition in the kidneys after ethylene glycol exposure. Renal calcium oxalate deposition in rats after ethylene glycol exposure has been shown to increase in the presence of high levels of dietary calcium (Ebisuno et al. 1987). Administration of phytin or citrate appears to inhibit calcium oxalate deposition in the renal tubules. Thus, phytin or citrate may be a useful dietary agent for the prevention of adverse renal effects after ethylene glycol ingestion, especially in the presence of high calcium levels. Therefore, some data exist on dietary factors that may influence ethylene glycol toxicity. Further studies on these factors and others that may be useful in a clinical setting would be helpful in increasing the number of treatments that are beneficial in reducing the toxic effects of ethylene glycol.

4-Methyl pyrazole, an alcohol dehydrogenase inhibitor, effectively blocks the metabolism of ethylene glycol to toxic intermediates, and has been shown to be effective in preventing renal effect of ethylene glycol after ingestion (Baud et al. 1987, 1988; Dial et al. 1989, 1994). Additional studies to identify other metabolic inhibitors would be useful in adding to the treatments available for reducing or preventing the toxic effects of ethylene glycol.

No studies related to reducing absorption of propylene glycol after inhalation or oral exposure were found. Studies on the dermal absorption of propylene glycol in rats indicate that absorption into the dermis is enhanced by the addition of fatty acids (Takeuchi et al. 1993, 1995). Thus, cleaning of the skin with a defatting solvent, followed by washing with water, may reduce absorption of propylene glycol after dermal exposure.

Toxicity studies of propylene glycol in laboratory animals can be found in the literature, but findings of adverse effects are rare. Clinical studies in the literature consist of infrequent sensitivity reactions, primarily to drug preparations, where pre-existing conditions requiring the drug come into play. There are two main reasons for that: 1) propylene glycol biodegradation proceeds via lactate to pyruvate in human metabolism, and 2) a significant amount of propylene glycol is excreted unchanged or as glucuronide conjugate via the renal pathway (Hannuksela and Forstrom 1978). Propylene glycol exhibits few of the toxic properties of ethylene glycol. Since it does cause metabolic acidosis, although to a lesser extent that ethylene glycol, correction of the acid-base imbalance would also be helpful in preventing subsequent effects, and the same therapies that are useful in preventing ethylene glycol acidosis would also be useful for propylene glycol. Since propylene glycol is significantly less toxic than ethylene glycol, extensive study of methods to reduce the possible toxic effects of exposure does not seem warranted.

2.9.3 Ongoing Studies

The following ongoing studies regarding the health effects of ethylene glycol and propylene glycol were reported .in the Federal Research in Progress File (FEDRIP 1995) database and in recent literature:

Alcohol and Pyrazole Reaction and Metabolism (in vitro). The principle investigator is Arthur Cederbaum, II from Mount Sinai School of Medicine, New York, New York. The objective is to study the biochemical and pharmacological properties of pyrazole and 4-methyl pyrazole and their enzymatic loci for metabolism, in relation to their use in ethylene glycol poisoning.

Cryopreservation of Bovine Oocytes Matured in vitro. The principal investigator is J. Parks from the Cornell University School of Animal Science, Ithaca, New York. The objective is to develop practical

procedures for the cryopreservation of developmentally competent bovine oocytes. Ethylene glycol will be used as one of the cryoprotective compounds.

Evaluation of ethylene glycol poisoning continues. In a recent publication, Hylander et al. (1995) suggest that patients with severe ethylene glycol intoxication resulting in severe acidosis, hyperkalemia, and coma upon admission to a hospital have a dismal prognosis, and that other factors are unimportant to the outcome. The authors suggest that large amounts of bicarbonate, alcohol, and hemodialysis be instituted immediately and maintained, and that the renal damage more closely resembles acute tubular necrosis rather than oxalate nephropathy.

Other studies in recent literature include a study of *in vitro* penetration of ethylene glycol through human and mouse skin (Sun et al. 1995). The study was undertaken to further define absorption of ethylene glycol through human and animal skin, since dermal exposure is the most common route for humans. Preliminary results indicate that human skin is 3040 times less permeable to ethylene glycol than mouse skin. In addition, absorption of a 50% aqueous solution is approximately twice as slow in both mice and humans, compared to absorption of undiluted ethylene glycol. The authors conclude that the potential toxicity resulting from cutaneous exposure to ethylene glycol would be significantly less for humans than predicted by dermal studies in mice. In addition, aqueous solutions pose less of a hazard for dermal exposure than does undiluted ethylene glycol. Camey et al. (1995) published preliminary results of a study designed to determine if glycolic acid acts as the proximate toxicant for ethylene glycol developmental toxicity in rat whole embryo culture. Rat embryos were cultured in media containing ethylene glycol or glycolic acid at concentrations equivalent to maternal plasma concentrations observed at a NOAEL, LOAEL, or teratogenic dose in viva. Ethylene glycol was without effect in culture. Glycolic acid inhibited embryo growth, and caused death. Dysmorphogenesis was observed at the higher dose. Lowering the pH in the media exacerbated the effects, The results of this study suggests that glycolic acid acts as an intrinsic developmental toxicant and through the induction of metabolic acidosis.

Regulation of Lipid Metabolism in High Producing Dairy Cattle. The principal investigator is R. Grummer from the University of Wisconsin School of Dairy Science in Madison, Wisconsin. The objective is to determine the regulation of lipid metabolism in adipose tissue, liver and mammary glands of high producing dairy cattle. Propylene glycol will be used for reducing plasma nonesterified fatty acids during feed restriction.

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Modifying Milk Fat Composition for Improved Manufacturing Qualities and Consumer Acceptability. The principal investigator is D. Palmquist from Ohio State University School of Animal Sciences in Wooster, Ohio. The objective is to identify and characterize important regulatory steps in fatty acid synthesis and desaturation and their positional distribution on glycerol in milk fat, and to quantify modification of milk fat composition by manipulating the diet of the cow. Propylene glycol will be used as an oral drench to modify energy balance.

Microbial Safety Criteria for Foods Contacting Reuse Water in Food. The principal investigator is A. Miller from the Eastern Regional Research Center in Wyndmoor, Pennsylvania. The objective is to identify microbiological risks to food by reuse water during slaughter and further processing, to study bacterial attachment mechanisms and develop approaches to dislodge or prevent adhesion of pathogens to food surfaces, and to investigate the potential for expanded applications of reuse water to the food plant environment. Propylene glycol will be evaluated in the control of microbial growth.

The Effect of Vitamin E on the Propylene Glycol-Induced Formation of Heinz Bodies. The principal investigator is Diane Hatchell from the Department of Veterans Affairs Medical Center, Durham, North Carolina. The objective is to test the efficacy of vitamin E as a means of inhibiting the propylene glycol-induced formation of Heinz bodies in cat blood.